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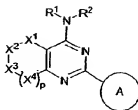
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(54) Title: CONDENSED PYRAMIDINE COMPOUNDS AS INHIBITORS OF VOLTAGE-GATED ION CHANNELS



(I)

(57) Abstract: The present invention relates to compounds of formula (I) useful as inhibitors of voltage-gated sodium channels. The invention also provides pharmaceutically acceptable compositions comprising the compounds of the invention and methods of using the compositions in the treatment of various disorders. Wherein R<sup>1</sup>, R<sup>2</sup>, X<sup>1</sup>-X<sup>4</sup>, P, and ring A are as defined in the present application.

## CONDENSED PYRIMIDINE COMPOUNDS AS INHIBITORS OF VOLTAGE-GATED ION CHANNELS

TECHNICAL FIELD OF THE INVENTION

[0001] The present invention relates to compounds useful as inhibitors of voltage-gated sodium channels and calcium channels. The invention also provides pharmaceutically acceptable compositions comprising the compounds of the invention and methods of using the compositions in the treatment of various disorders.

BACKGROUND OF THE INVENTION

[0002] Na channels are central to the generation of action potentials in all excitable cells such as neurons and myocytes. They play key roles in excitable tissue including brain, smooth muscles of the gastrointestinal tract, skeletal muscle, the peripheral nervous system, spinal cord and airway. As such they play key roles in a variety of disease states such as epilepsy (See, Moulard, B. and D. Bertrand (2002) "Epilepsy and sodium channel blockers" Expert Opin. Ther. Patents 12(1): 85-91)), pain (See, Waxman, S. G., S. Dib-Hajj, et al. (1999) "Sodium channels and pain" Proc Natl Acad Sci U S A 96(14): 7635-9 and Waxman, S. G., T. R. Cummins, et al. (2000) "Voltage-gated sodium channels and the molecular pathogenesis of pain: a review" J Rehabil Res Dev 37(5): 517-28), myotonia (See, Meola, G. and V. Sansone (2000) "Therapy in myotonic disorders and in muscle channelopathies" Neurol Sci 21(5): S953-61 and Mankodi, A. and C. A. Thornton (2002) "Myotonic syndromes" Curr Opin Neurol 15(5): 545-52), ataxia (See, Meisler, M. H., J. A. Kearney, et al. (2002) "Mutations of voltage-gated sodium channels in movement disorders and epilepsy" Novartis Found Symp 241: 72-81), multiple sclerosis (See, Black, J. A., S. Dib-Hajj, et al. (2000) "Sensory neuron-specific sodium channel SNS is abnormally expressed in the brains of mice with experimental allergic encephalomyelitis and humans with multiple sclerosis" Proc Natl Acad Sci U S A 97(21): 11598-602, and Renganathan, M., M. Gelderblom, et al. (2003) "Expression of Na(v)1.8 sodium channels perturbs the firing patterns of cerebellar purkinje cells" Brain Res 959(2): 235-42), irritable bowel (See, Su, X., R. E. Wachtel, et al. (1999) "Capsaicin sensitivity and voltage-gated sodium currents in colon

sensory neurons from rat dorsal root ganglia" Am J Physiol 277(6 Pt 1): G1180-8, and Laird, J. M., V. Souslova, et al. (2002) "Deficits in visceral pain and referred hyperalgesia in Nav1.8 (SNS/PN3)- null mice" J Neurosci 22(19): 8352-6, urinary incontinence and visceral pain (See, Yoshimura, N., S. Seki, et al. (2001) "The involvement of the tetrodotoxin-resistant sodium channel Nav1.8 (PN3/SNS) in a rat model of visceral pain" J Neurosci 21(21): 8690-6, as well as an array of psychiatry dysfunctions such as anxiety and depression (See, Hurley, S. C. (2002) "Lamotrigine update and its use in mood disorders" Ann Pharmacother 36(5): 860-73).

[0003] Voltage gated Na channels comprise a gene family consisting of 9 different subtypes (Nav1.1-Nav1.9). As shown in Table 1, these subtypes show tissue specific localization and functional differences (See, Goldin, A. L. (2001) "Resurgence of sodium channel research" Annu Rev Physiol 63: 871-94). Three members of the gene family (Nav1.8, 1.9, 1.5) are resistant to block by the well-known Na channel blocker TTX, demonstrating subtype specificity within this gene family. Mutational analysis has identified glutamate 387 as a critical residue for TTX binding (See, Noda, M., H. Suzuki, et al. (1989) "A single point mutation confers tetrodotoxin and saxitoxin insensitivity on the sodium channel II" FEBS Lett 259(1): 213-6).

[0004] Table 1 (Abbreviations: CNS = central nervous system, PNS = peripheral nervous system, DRG = dorsal root ganglion, TG = Trigeminal ganglion):

Na Isoform	Tissue	TTX IC50	Indications
Nav1.1	CNS, PNS soma of neurons	10nM	Pain, Epilepsy, neurodegeneration
Nav1.2	CNS, high in axons	10nM	Neurodegeneration Epilepsy
Nav1.3	CNS, embryonic, injured nerves	15nM	Pain, Epilepsy
Nav1.4	Skeletal muscle	25nM	Myotonia
Nav1.5	Heart	2μM	Arrhythmia, long QT
Nav1.6	CNS widespread, most abundant	6nM	Pain, movement disorders

Na Isoform	Tissue	TTX IC50	Indications
NaV1.7	PNS, DRG, terminals neuroendocrine	25nM	Pain, Neuroendocrine disorders
NaV1.8	PNS, small neurons in DRG & TG	>50μM	Pain
NaV1.9	PNS, small neurons in DRG & TG	1μM	Pain

**[0005]** In general, voltage-gated sodium channels (NaVs) are responsible for initiating the rapid upstroke of action potentials in excitable tissue in nervous system, which transmit the electrical signals that compose and encode normal and aberrant pain sensations. Antagonists of NaV channels can attenuate these pain signals and are useful for treating a variety of pain conditions, including but not limited to acute, chronic, inflammatory, and neuropathic pain. Known NaV antagonists, such as TTX, lidocaine (See, Mao, J. and L. L. Chen (2000) "Systemic lidocaine for neuropathic pain relief" Pain 87(1): 7-17.) bupivacaine, phenytoin (See, Jensen, T. S. (2002) "Anticonvulsants in neuropathic pain: rationale and clinical evidence" Eur J Pain 6 (Suppl A): 61-8), lamotrigine (See, Rozen, T. D. (2001) "Antiepileptic drugs in the management of cluster headache and trigeminal neuralgia" Headache 41 Suppl 1: S25-32 and Jensen, T. S. (2002) "Anticonvulsants in neuropathic pain: rationale and clinical evidence" Eur J Pain 6 (Suppl A): 61-8.), and carbamazepine (See, Backonja, M. M. (2002) "Use of anticonvulsants for treatment of neuropathic pain" Neurology 59(5 Suppl 2): S14-7), have been shown to be useful attenuating pain in humans and animal models.

**[0006]** Hyperalgesia (extreme sensitivity to something painful) that develops in the presence of tissue injury or inflammation reflects, at least in part, an increase in the excitability of high-threshold primary afferent neurons innervating the site of injury. Voltage sensitive sodium channels activation is critical for the generation and propagation of neuronal action potentials. There is a growing body of evidence indicating that modulation of NaV currents is an endogenous mechanism used to control neuronal excitability (See, Goldin, A. L. (2001) "Resurgence of sodium channel research" Annu Rev Physiol 63: 871-94.). Several kinetically and pharmacologically distinct voltage-gated sodium channels are found in dorsal root ganglion (DRG) neurons. The TTX-resistant current is insensitive to micromolar concentrations of

tetrodotoxin, and displays slow activation and inactivation kinetics and a more depolarized activation threshold when compared to other voltage-gated sodium channels. TTX-resistant sodium currents are primarily restricted to a subpopulation of sensory neurons likely to be involved in nociception. Specifically, TTX-resistant sodium currents are expressed almost exclusively in neurons that have a small cell-body diameter, and give rise to small-diameter slow-conducting axons and that are responsive to capsaicin. A large body of experimental evidence demonstrates that TTX-resistant sodium channels are expressed on C-fibers and are important in the transmission of nociceptive information to the spinal cord.

[0007] Intrathecal administration of antisense oligo-deoxynucleotides targeting a unique region of the TTX-resistant sodium channel (Nav1.8) resulted in a significant reduction in PGE<sub>2</sub>-induced hyperalgesia (See, Khasar, S. G., M. S. Gold, et al. (1998) "A tetrodotoxin-resistant sodium current mediates inflammatory pain in the rat" Neurosci Lett 256(1): 17-20). More recently, a knockout mouse line was generated by Wood and colleagues, which lacks functional Nav1.8. The mutation has an analgesic effect in tests assessing the animal's response to the inflammatory agent carrageenan (See, Akopian, A. N., V. Souslova, et al. (1999) "The tetrodotoxin-resistant sodium channel SNS has a specialized function in pain pathways" Nat Neurosci 2(6): 541-8.). In addition, deficit in both mechano- and thermoreception were observed in these animals. The analgesia shown by the Nav1.8 knockout mutants is consistent with observations about the role of TTX-resistant currents in nociception.

[0008] Immunohistochemical, in-situ hybridization and in-vitro electrophysiology experiments have all shown that the sodium channel Nav1.8 is selectively localized to the small sensory neurons of the dorsal root ganglion and trigeminal ganglion (See, Akopian, A. N., L. Sivilotti, et al. (1996) "A tetrodotoxin-resistant voltage-gated sodium channel expressed by sensory neurons" Nature 379(6562): 257-62.). The primary role of these neurons is the detection and transmission of nociceptive stimuli. Antisense and immunohistochemical evidence also supports a role for Nav1.8 in neuropathic pain (See, Lai, J., M. S. Gold, et al. (2002) "Inhibition of neuropathic pain by decreased expression of the tetrodotoxin-resistant sodium channel, Nav1.8" Pain 95(1-2): 143-52, and Lai, J., J. C. Hunter, et al. (2000) "Blockade of neuropathic pain by antisense targeting of tetrodotoxin-resistant sodium channels in sensory neurons" Methods Enzymol 314: 201-13.). Nav1.8 protein is upregulated along uninjured C-fibers adjacent to the nerve injury. Antisense treatment prevents the redistribution of Nav1.8 along the

nerve and reverses neuropathic pain. Taken together the gene-knockout and antisense data support a role for NaV1.8 in the detection and transmission of inflammatory and neuropathic pain.

[0009] In neuropathic pain states there is a remodeling of Na channel distribution and subtype. In the injured nerve, expression of NaV1.8 and NaV1.9 are greatly reduced whereas expression of the TTX sensitive subunit NaV1.3 is significantly upregulated in animal models of neuropathic pain (See, Dib-Hajj, S. D., J. Fjell, et al. (1999) "Plasticity of sodium channel expression in DRG neurons in the chronic constriction injury model of neuropathic pain." Pain 83(3): 591-600 and Kim, C.H., Youngsuk, O., et al. (2001) "The changes in expression of three subtypes of TTX sensitive sodium channels in sensory neurons after spinal nerve ligation". Mol. Brain Res. 95:153-61.) The timecourse of the increase in NaV1.3 parallels the appearance of allodynia in animal models subsequent to nerve injury. Up-regulation of Nav1.3 transcription is also observed in a rat model of diabetic neuropathy. (See, Craner, M.J., Klein, J.P. et al. (2002) "Changes of sodium channel expression in experimental painful diabetic neuropathy." Ann Neurol. 52(6): 786-92. The biophysics of the NaV1.3 channel is distinctive in that it shows very fast repriming after inactivation following an action potential. This allows for sustained rates of high firing as is often seen in the pathophysiological activity accompanying neuropathic pain (See, Cummins, T. R., F. Aglieco, et al. (2001) "Nav1.3 sodium channels: rapid repriming and slow closed-state inactivation display quantitative differences after expression in a mammalian cell line and in spinal sensory neurons" J. Neurosci. 21(16): 5952-61.). Human NaV1.3 channel proteins are expressed in the central and peripheral systems of man. (See, Chen, Y.H., Dale, T.J., et al. (2000) "Cloning, distribution and functional analysis of the type III sodium channel from human brain." Eur. J. Neurosci. 12: 4281-89). Furthermore, in the periphery, NaV1.3 channel proteins are detectable in injured but not uninjured human nerves indicating that NaV1.3 plays important physiological roles under pathophysiological conditions in humans as well. Given the strong correlation between increased NaV1.3 channel expression and neuronal hyperexcitability, inhibitors of NaV1.3 channels, and in particular selective ones, might therefore provide efficacious therapeutic agents with less-severe side effects than nonselective Na<sup>+</sup> channel inhibitors in the treatment of painful neuropathies. Similarly, NaV1.3 overexpression may also be associated with increased epileptic neuronal activity as it is significantly upregulated in hippocampal pyramidal neurons of epileptic humans (See, Whitaker, W.R.J., Faull, M., et al.

(2001) "Changes in the mRNAs encoding voltage-gated sodium channel types II and III in human epileptic hippocampus." *Neurosci.* **106**(2): 275-285.; inhibitors with some selectivity against Nav1.3 could also be particularly attractive anticonvulsants and neuroprotectants.

[0010] Nav1.9 is similar to Nav1.8 as it is selectively localized to small sensory neurons of the dorsal root ganglion and trigeminal ganglion (See, Fang, X., L. Djouhri, et al. (2002). "The presence and role of the tetrodotoxin-resistant sodium channel Na(v)1.9 (NaN) in nociceptive primary afferent neurons." *J Neurosci* **22**(17): 7425-33.). It has a slow rate of inactivation and left-shifted voltage dependence for activation (See, Dib-Hajj, S., J. A. Black, et al. (2002) "NaN/Nav1.9: a sodium channel with unique properties" *Trends Neurosci* **25**(5): 253-9.). These two biophysical properties allow Nav1.9 to play a role in establishing the resting membrane potential of nociceptive neurons. The resting membrane potential of Nav1.9 expressing cells is in the -55 to -50mV range compared to -65mV for most other peripheral and central neurons. This persistent depolarization is in large part due to the sustained low-level activation of Nav1.9 channels. This depolarization allows the neurons to more easily reach the threshold for firing action potentials in response to nociceptive stimuli. Compounds that block the Nav1.9 channel may play an important role in establishing the set point for detection of painful stimuli.

[0011] In chronic pain states, nerve and nerve ending can become swollen and hypersensitive exhibiting high frequency action potential firing with mild or even no stimulation. These pathologic nerve swellings are termed neuromas and the primary Na channels expressed in them are Nav1.8 and Nav1.7 (See, Kretschmer, T., L. T. Happel, et al. (2002) "Accumulation of PN1 and PN3 sodium channels in painful human neuroma- evidence from immunocytochemistry" *Acta Neurochir (Wien)* **144**(8): 803-10; discussion 810.). Nav1.6 and Nav1.7 are also expressed in dorsal root ganglion neurons and contribute to the small TTX sensitive component seen in these cells. Nav1.7 in particular may therefore be a potential pain target in addition to its role in neuroendocrine excitability (See, Klugbauer, N., L. Lacinova, et al. (1995) "Structure and functional expression of a new member of the tetrodotoxin-sensitive voltage-activated sodium channel family from human neuroendocrine cells" *Embo J* **14**(6): 1084-90).

[0012] Nav1.1 (See, Sugawara, T., E. Mazaki-Miyazaki, et al. (2001) "Nav1.1 mutations cause febrile seizures associated with afebrile partial seizures." *Neurology* **57**(4): 703-5.) and Nav1.2 (See, Sugawara, T., Y. Tsurubuchi, et al. (2001) "A missense mutation of the Na+

channel alpha II subunit gene Na(v)1.2 in a patient with febrile and afebrile seizures causes channel dysfunction" Proc Natl Acad Sci U S A 98(11): 6384-9) have been linked to epilepsy conditions including febrile seizures. There are over 9 genetic mutations in NaV1.1 associated with febrile seizures (See, Meisler, M. H., J. A. Kearney, et al. (2002) "Mutations of voltage-gated sodium channels in movement disorders and epilepsy" Novartis Found Symp 241: 72-81)

[0013] Antagonists for NaV1.5 have been developed and used to treat cardiac arrhythmias. A gene defect in NaV1.5 that produces a larger noninactivating component to the current has been linked to long QT in man and the orally available local anesthetic mexilitine has been used to treat this condition (See, Wang, D. W., K. Yazawa, et al. (1997) "Pharmacological targeting of long QT mutant sodium channels." J Clin Invest 99(7): 1714-20).

[0014] Several Na channel blockers are currently used or being tested in the clinic to treat epilepsy (See, Moulard, B. and D. Bertrand (2002) "Epilepsy and sodium channel blockers" Expert Opin. Ther. Patents 12(1): 85-91.); acute (See, Wiffen, P., S. Collins, et al. (2000) "Anticonvulsant drugs for acute and chronic pain" Cochrane Database Syst Rev 3), chronic (See, Wiffen, P., S. Collins, et al. (2000) "Anticonvulsant drugs for acute and chronic pain" Cochrane Database Syst Rev 3, and Guay, D. R. (2001) "Adjunctive agents in the management of chronic pain" Pharmacotherapy 21(9): 1070-81), inflammatory (See, Gold, M. S. (1999) "Tetrodotoxin-resistant Na<sup>+</sup> currents and inflammatory hyperalgesia." Proc Natl Acad Sci U S A 96(14): 7645-9), and neuropathic pain (See, Strichartz, G. R., Z. Zhou, et al. (2002) "Therapeutic concentrations of local anaesthetics unveil the potential role of sodium channels in neuropathic pain" Novartis Found Symp 241: 189-201, and Sandner-Kiesling, A., G. Rumpold Seitlinger, et al. (2002) "Lamotrigine monotherapy for control of neuralgia after nerve section" Acta Anaesthesiol Scand 46(10): 1261-4); cardiac arrhythmias (See, An, R. H., R. Bangalore, et al. (1996) "Lidocaine block of LQT-3 mutant human Na<sup>+</sup> channels" Circ Res 79(1): 103-8, and Wang, D. W., K. Yazawa, et al. (1997) "Pharmacological targeting of long QT mutant sodium channels" J Clin Invest 99(7): 1714-20); neuroprotection (See, Taylor, C. P. and L. S. Narasimhan (1997) "Sodium channels and therapy of central nervous system diseases" Adv Pharmacol 39: 47-98) and as anesthetics (See, Strichartz, G. R., Z. Zhou, et al. (2002) "Therapeutic concentrations of local anaesthetics unveil the potential role of sodium channels in neuropathic pain." Novartis Found Symp 241: 189-201).



[0015] Voltage-gated calcium channels are membrane-spanning, multi-subunit proteins that open in response to membrane depolarization, allowing Ca entry from the extracellular milieu. Calcium channels were initially classified based on the time and voltage-dependence of channel opening and on the sensitivity to pharmacological block. The categories were low-voltage activated (primarily T-type) and high-voltage activated (L,N,P,Q or R-type). This classification scheme was replaced by a nomenclature based upon the molecular subunit composition, as summarized in Table I (Hockerman, G. H., et. al. (1997) Annu. Rev. Pharmacol. Toxicol. 37: 361-96; Striessnig, J. (1999) Cell. Physiol. Biochem. 9: 242-69). There are four primary subunit types that make up calcium channels -  $\alpha_1$ ,  $\alpha_2\delta$ ,  $\beta$  and  $\gamma$  (See, e.g., De Waard et al. Structural and functional diversity of voltage-activated calcium channels. In *Ion Channels*, (ed. T. Narahashi) 41-87, (Plenum Press, New York, 1996)). The  $\alpha_1$  subunit is the primary determinant of the pharmacological properties and contains the channel pore and voltage sensor (Hockerman, G. H., et. al. (1997) Annu. Rev. Pharmacol. Toxicol. 37: 361-96; Striessnig, J. (1999) Cell. Physiol. Biochem. 9: 242-69). Ten isoforms of the  $\alpha_1$  subunit are known, as indicated in Table I. The  $\alpha_2\delta$  subunit consists of two disulfide linked subunits,  $\alpha_2$ , which is primarily extracellular and a transmembrane  $\delta$  subunit. Four isoforms of  $\alpha_2\delta$  are known,  $\alpha_2\delta$ -1,  $\alpha_2\delta$ -2,  $\alpha_2\delta$ -3 and  $\alpha_2\delta$ -4. The  $\beta$  subunit is a non-glycosylated cytoplasmic protein that binds to the  $\alpha_1$  subunit. Four isoforms are known, termed  $\beta_1$  to  $\beta_4$ . The  $\gamma$  subunit is a transmembrane protein that has been biochemically isolated as a component of Ca<sub>v</sub>1 and Ca<sub>v</sub>2 channels. At least 8 isoforms are known ( $\gamma_1$  to  $\gamma_8$ ) (Kang, M.G. and K. P. Campbell (2003) J. Biol. Chem. 278: 21315-8). The nomenclature for voltage-gated calcium channels is based upon the content of the  $\alpha_1$  subunit, as indicated in Table I. Each type of  $\alpha_1$  subunit can associate with a variety of  $\beta$ ,  $\alpha_2\delta$  or  $\gamma$  subunits, so that each Ca<sub>v</sub> type corresponds to many different combinations of subunits.

Cav Nomenclature	$\alpha_1$ subunit	Pharmacological name
Ca <sub>v</sub> 1.1	$\alpha_{1S}$	L-type
Ca <sub>v</sub> 1.2	$\alpha_{1C}$	L-type
Ca <sub>v</sub> 1.3	$\alpha_{1D}$	L-type
Ca <sub>v</sub> 1.4	$\alpha_{1F}$	
Ca <sub>v</sub> 2.1	$\alpha_{1A}$	P- or Q-type
Ca <sub>v</sub> 2.2	$\alpha_{1B}$	N-type
Ca <sub>v</sub> 2.3	$\alpha_{1E}$	R-type
Ca <sub>v</sub> 3.1	$\alpha_{1G}$	T-type
Ca <sub>v</sub> 3.2	$\alpha_{1H}$	T-type
Ca <sub>v</sub> 3.3	$\alpha_{1I}$	T-type

**[0016]** Ca<sub>v</sub>2 currents are found almost exclusively in the central and peripheral nervous system and in neuroendocrine cells and constitute the predominant forms of presynaptic voltage-gated calcium current. Presynaptic action potentials cause channel opening and neurotransmitter release is steeply dependent upon the subsequent calcium entry. Thus, Ca<sub>v</sub>2 channels play a central role in mediating neurotransmitter release.

**[0017]** Ca<sub>v</sub>2.1 and Ca<sub>v</sub>2.2 contain high-affinity binding sites for the peptide toxins  $\omega$ -conotoxin-MV1C and  $\omega$ -conotoxin-GVIA, respectively, and these peptides have been used to determine the distribution and function of each channel type. Ca<sub>v</sub>2.2 is highly expressed at the presynaptic nerve terminals of neurons from the dorsal root ganglion and neurons of lamina I and II of the dorsal horn (Westenbroek, R. E., et al. (1998) *J. Neurosci.* 18: 6319-30; Cizkova, D, et al. (2002) *Exp. Brain Res.* 147: 456-63). Ca<sub>v</sub>2.2 channels are also found in presynaptic terminals between second and third order interneurons in the spinal cord. Both sites of neurotransmission are very important in relaying pain information to the brain.

**[0018]** Pain can be roughly divided into three different types: acute, inflammatory, and neuropathic. Acute pain serves an important protective function in keeping the organism safe from stimuli that may produce tissue damage. Severe thermal, mechanical, or chemical inputs have the potential to cause severe damage to the organism if unheeded. Acute pain serves to quickly remove the individual from the damaging environment. Acute pain by its very nature

generally is short lasting and intense. Inflammatory pain, on the other hand, may last for much longer periods of time and its intensity is more graded. Inflammation may occur for many reasons including tissue damage, autoimmune response, and pathogen invasion. Inflammatory pain is mediated by a variety of agents that are released during inflammation, including substance P, histamines, acid, prostaglandin, bradykinin, CGRP, cytokines, ATP, and other agents (Julius, D. and A. I. Basbaum (2001) Nature 413 (6852): 203-10). The third class of pain is neuropathic and involves nerve damage arising from nerve injury or viral infection and results in reorganization of neuronal proteins and circuits yielding a pathologic "sensitized" state that can produce chronic pain lasting for years. This type of pain provides no adaptive benefit and is particularly difficult to treat with existing therapies.

**[0019]** Pain, particularly neuropathic and intractable pain is a large unmet medical need. Millions of individuals suffer from severe pain that is not well controlled by current therapeutics. The current drugs used to treat pain include NSAIDs, COX-2 inhibitors, opioids, tricyclic antidepressants, and anticonvulsants. Neuropathic pain has been particularly difficult to treat as it does not respond well to opioids until high doses are reached. Gabapentin is currently the most widely used therapeutic for the treatment of neuropathic pain, although it works in only 60% of patients and has modest efficacy. The drug is generally safe, although sedation is an issue at higher doses.

**[0020]** Validation of Cav2.2 as a target for the treatment of neuropathic pain is provided by studies with ziconotide (also known as  $\omega$ -conotoxin-MVIIA), a selective peptide blocker of this channel (Bowersox, S.S., et al. (1996) J. Pharmacol. Exp. Ther. 279: 1243-9; Jain, K.K. (2000) Exp. Opin. Invest. Drugs 9: 2403-10; Vanegas, H. and H. Schaible (2000) Pain 85: 9-18). In man, intrathecal infusion of Ziconotide is effective for the treatment of intractable pain, cancer pain, opioid resistant pain, and neuropathic pain. The toxin has an 85% success rate for the treatment of pain in humans with a greater potency than morphine. An orally available antagonist of Cav2.2 should have similar efficacy without the need for intrathecal infusion. Cav2.1 and Cav2.3 are also in neurons of nociceptive pathways and antagonists of these channels could be used to treat pain.

**[0021]** Antagonists of Cav2.1, Cav2.2 or Cav2.3 should also be useful for treating other pathologies of the central nervous system that apparently involve excessive calcium entry. Cerebral ischaemia and stroke are associated with excessive calcium entry due to depolarization

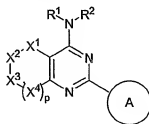
of neurons. The  $\text{Ca}_v2.2$  antagonist ziconotide is effective in reducing infarct size in a focal ischemia model using laboratory animals, suggesting that  $\text{Ca}_v2.2$  antagonists could be used for the treatment of stroke. Likewise, reducing excessive calcium influx into neurons may be useful for the treatment of epilepsy, traumatic brain injury, Alzheimer's disease, multi-infarct dementia and other classes of dementia, amyotrophic lateral sclerosis, amnesia, or neuronal damage caused by poison or other toxic substances.

[0022]  $\text{Ca}_v2.2$  also mediates release of neurotransmitters from neurons of the sympathetic nervous system and antagonists could be used to treat cardiovascular diseases such as hypertension, cardiac arrhythmia, angina pectoris, myocardial infarction, and congestive heart failure.

[0023] Unfortunately, as described above, the efficacy of currently used sodium channel blockers and calcium channel blockers for the disease states described above has been to a large extent limited by a number of side effects. These side effects include various CNS disturbances such as blurred vision, dizziness, nausea, and sedation as well more potentially life threatening cardiac arrhythmias and cardiac failure. Accordingly, there remains a need to develop additional Na channel antagonists, and Ca channel antagonists preferably those with higher potency and fewer side effects.

### SUMMARY OF THE INVENTION

[0024] It has now been found that compounds of this invention, and pharmaceutically acceptable compositions thereof, are useful as inhibitors of voltage-gated sodium channels. These compounds have the general formula I:



I

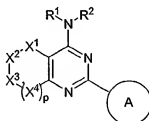
or a pharmaceutically acceptable salt thereof, wherein  $\text{R}^1$ ,  $\text{R}^2$ ,  $\text{X}^1$ ,  $\text{X}^2$ ,  $\text{X}^3$ ,  $\text{X}^4$ ,  $p$ , and Ring A are as defined below.

[0025] These compounds, and pharmaceutically acceptable compositions thereof, are useful for treating or lessening the severity of a variety of diseases, disorders, or conditions, including, but not limited to, acute, chronic, neuropathic, or inflammatory pain, arthritis, migraine, cluster headaches, trigeminal neuralgia, herpetic neuralgia, general neuralgias, epilepsy or epilepsy conditions, neurodegenerative disorders, psychiatric disorders such as anxiety and depression, myotonia, arrhythmia, movement disorders, neuroendocrine disorders, ataxia, multiple sclerosis, irritable bowel syndrome, and incontinence.

### DETAILED DESCRIPTION OF THE INVENTION

[0026] *I. General Description of Compounds of the Invention:*

[0027] The present invention relates to compound of formula I useful as inhibitor of voltage-gated sodium channels:



I

or a pharmaceutically acceptable salt thereof, wherein:

p is 0, 1 or 2;

X<sup>1</sup>, X<sup>2</sup>, X<sup>3</sup> and X<sup>4</sup> are each independently selected from NR<sup>3</sup>, C=O, CHR<sup>4</sup>, S, O, S=O, or SO<sub>2</sub>, as valency and stability permit;

R<sup>1</sup> and R<sup>2</sup> are each independently hydrogen, or an optionally substituted group selected from C<sub>1-6</sub> aliphatic, a 5-6 membered aryl ring having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or R<sup>1</sup> and R<sup>2</sup>, taken together with the nitrogen atom to which they are bound, form an optionally substituted 3-8 membered heterocyclyl or heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein R<sup>1</sup>, R<sup>2</sup>, or any ring formed by R<sup>1</sup> and R<sup>2</sup> taken together, are

each independently optionally substituted at one or more carbon atoms with 0-4 occurrences of  $-R^5$ , and at one or more substitutable nitrogen atoms with  $-R^6$ ;

Ring A is a 5-6 membered monocyclic or 8-10 membered bicyclic aryl ring having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, optionally substituted at one or more carbon atoms with 0-5 occurrences of  $-R^7$ , and at one or more substitutable nitrogen atoms with  $-R^8$ ;

each occurrence of  $R^4$ ,  $R^5$ , and  $R^7$  is independently  $Q-R^X$ ; wherein Q is a bond or is a  $C_1-C_6$  alkylidene chain wherein up to two non-adjacent methylene units of Q are optionally and independently replaced by CO,  $CO_2$ , COCO, CONR, OCONR, NRNR, NRNR $CO$ , NR $CO$ , NR $CO_2$ , NRCONR, SO,  $SO_2$ , NR $SO_2$ ,  $SO_2NR$ , NR $SO_2NR$ , O, S, or NR;

each occurrence of  $R^X$  is independently selected from R', halogen,  $NO_2$ , or CN;

each occurrence of R is independently selected from hydrogen or an optionally substituted  $C_{1-6}$  aliphatic group;

each occurrence of R' is independently selected from hydrogen or an optionally substituted group selected from  $C_{1-8}$  aliphatic,  $C_{6-10}$  aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclyl ring having 3-10 ring atoms, or wherein R and R' taken together with the atom(s) to which they are bound, or two occurrences of R' taken together with the atom(s) to which they are bound, form a 5-8 membered cycloalkyl, heterocyclyl, aryl, or heteroaryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and

each occurrence of  $R^3$ ,  $R^6$  or  $R^8$  is independently R',  $-COR'$ ,  $-CO_2(C_{1-6}$  aliphatic),  $-CON(R')_2$ , or  $-SO_2R'$ .

[0028] In certain embodiments, for compounds of the invention as described generally above and herein:

- a)  $R^1$  is not hydrogen when  $R^2$  is optionally substituted indazol-3-yl;
- b)  $R^1$  is not hydrogen when  $R^2$  is optionally substituted pyrazol-3-yl;
- c)  $R^1$  is not hydrogen when  $R^2$  is 1,2,4-triazol-3-yl;
- d) when p is 1, then:
  - i) when  $R^1$  and  $R^2$ , taken together with the nitrogen atom, is N-morpholino, and Ring A is unsubstituted phenyl, then  $X^1$ ,  $X^2$ ,  $X^3$  and  $X^4$  are not, respectively:
    - 1)  $CH_2$ ,  $CH(CH_2)Ph$ ,  $NR^3$ , and  $CHCH_3$ ;

- 2)  $\text{CH}_2$ ,  $\text{CH}_2$ ,  $\text{CH}_2$ , and S;
  - 3)  $\text{CH}_2$ , S,  $\text{CH}_2$ , and S;
  - 4)  $\text{CH}_2$ ,  $\text{CH}_2$ , S, and  $\text{CH}_2$ ;
  - 5)  $\text{CH}_2$ ,  $\text{CHMe}$ , S, and  $\text{CH}_2$ ; or
  - 6)  $\text{CHMe}$ ,  $\text{CH}_2$ ,  $\text{N}(\text{CH}_2)\text{Ph}$ , and  $\text{CH}_2$ ;
- ii)  $\text{R}^1$  is not hydrogen, and  $\text{R}^2$  is not  $\text{CH}_2\text{Ph}$ ,  $(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{OH}$ , or  $-\text{CH}_2(1,3\text{-benzodioxol-5-yl})$  when ring A is imidazol-1-yl;
- iii) when  $\text{R}^1$  and  $\text{R}^2$ , taken together with the nitrogen atom, is N-piperidinyl then:
- 1) when  $\text{X}^1$ ,  $\text{X}^2$  and  $\text{X}^3$  are  $\text{CH}_2$ , and  $\text{X}^4$  is S, then Ring A is not unsubstituted phenyl; and
  - 2) when  $\text{X}^1$ ,  $\text{X}^2$  and  $\text{X}^4$  are  $\text{CH}_2$ ; and  $\text{X}^3$  is S, then Ring A is not unsubstituted phenyl;
- iv) when  $\text{R}^1$  and  $\text{R}^2$ , taken together with the nitrogen atom, is N-piperizinyl,  $\text{X}^1$ ,  $\text{X}^2$  and  $\text{X}^3$  are  $\text{CH}_2$ , and  $\text{X}^4$  is S, then Ring A is not 3- $\text{NO}_2\text{Ph}$ , 4-pyridinyl, or unsubstituted phenyl;
- v) when one of  $\text{X}^1$ ,  $\text{X}^2$ ,  $\text{X}^3$  or  $\text{X}^4$  is  $\text{NR}^3$  and the others of  $\text{X}^1$ ,  $\text{X}^2$ ,  $\text{X}^3$  or  $\text{X}^4$  are each  $\text{CH}_2$ , and  $\text{R}^1$  and  $\text{R}^2$  are each Me, H,  $\text{CH}_2\text{Ph}$ , or  $(\text{CH}_2)_2\text{NMe}_2$ , then Ring A is not pyrid-2-yl substituted at the 6-position;
- vi) when  $\text{X}^1$ ,  $\text{X}^2$ , and  $\text{X}^3$  are each  $\text{CH}_2$ ,  $\text{X}^4$  is S,  $\text{R}^1$  is H, and  $\text{R}^2$  is  $-\text{CH}_2-\text{C}=\text{CH}_2$ , then Ring A is not unsubstituted phenyl;
- vii) when  $\text{X}^1$  is  $\text{NMe}$ ;  $\text{X}^2$ ,  $\text{X}^3$  and  $\text{X}^4$  are each  $\text{CH}_2$ ,  $\text{R}^1$  is H, and  $\text{R}^2$  is unsubstituted phenyl, then Ring A is not unsubstituted phenyl; and
- viii) when  $\text{X}^1$ ,  $\text{X}^2$  and  $\text{X}^4$  are each  $\text{CH}_2$ ,  $\text{X}^3$  is S,  $\text{R}^1$  and  $\text{R}^2$  are each Me, then Ring A is not unsubstituted phenyl; and
- c) when p is 0, then:
- i) when  $\text{X}^1$  is  $\text{CH}_2$ ,  $\text{X}^2$  is  $\text{NR}^3$ ,  $\text{X}^3$  is  $\text{C}=\text{O}$ ; or  $\text{X}^1$  is  $\text{C}=\text{O}$ ,  $\text{X}^2$  is  $\text{CHR}^4$ , and  $\text{X}^3$  is  $\text{NR}^3$ ; or  $\text{X}^2$  is  $\text{NR}^3$ ,  $\text{X}^2$  is  $\text{C}=\text{O}$ , and  $\text{X}^3$  is  $\text{CHR}^4$ ; or  $\text{X}^1$  is  $\text{CH}_2$ ,  $\text{X}^2$  is O, and  $\text{X}^3$  is  $\text{C}=\text{O}$ , then when  $\text{R}^1$  is hydrogen and  $\text{R}^2$  is unsubstituted phenyl or  $-\text{CH}_2\text{CH}_2\text{Cl}$ , or when  $\text{R}^1$  and  $\text{R}^2$ , taken together form optionally substituted piperazinyl, morpholino, piperidinyl, or pyrrolidinyl, then Ring A is not optionally substituted piperidinyl, piperazinyl, morpholino, or pyrrolidinyl;

- ii) when  $X^1$  is  $\text{CHR}^4$ ,  $X^2$  is  $\text{SO}_2$ , and  $X^3$  is  $\text{CHR}^4$ , and  $R^1$  and  $R^2$ , taken together are piperazinyl, then Ring A is not unsubstituted phenyl;
- iii) when  $X^1$  and  $X^2$  are  $\text{CHR}^4$ ,  $X^3$  is O,  $R^1$  is hydrogen, and  $R^2$  is  $-\text{C}(=\text{O})\text{CH}_3$ , then Ring A is not substituted furyl;
- iv) when  $X^1$  is S,  $X^2$  is  $\text{CHR}^4$ ,  $X^3$  is  $\text{CHR}^4$ ; or  $X^1$  is  $\text{CHR}^4$ ,  $X^2$  is S, and  $X^3$  is  $\text{CHR}^4$ ; or  $X^1$  and  $X^2$  are  $\text{CHR}^4$  and  $X^3$  is S, then Ring A is not optionally substituted N-linked morpholino, pyrrolidinyl, piperazinyl, piperidinyl, or is not unsubstituted phenyl or cyclopropyl;
- v) when  $X^1$  is  $\text{CHR}^4$ ,  $X^2$  is  $\text{NR}^3$ ,  $X^3$  is  $\text{CHR}^4$ , and  $R^1$  and  $R^2$  are both methyl, then Ring A is not 6-methyl-2-pyridyl;
- vi) when  $X^1$  is  $\text{NR}^3$ ,  $X^2$  is  $\text{C}=\text{O}$ ,  $X^3$  is  $\text{NR}^3$ , and  $R^1$  and  $R^2$  are both methyl, then Ring A is not unsubstituted phenyl; and
- vii) when  $X^1$  and  $X^2$  are  $\text{CHR}^4$ ,  $X^3$  is  $\text{NR}^3$ ,  $R^1$  is hydrogen, and  $R^2$  is unsubstituted phenyl, then Ring A is not unsubstituted phenyl.

**[0029]** In certain other embodiments, for compounds of the invention as described generally above and herein:

- a) when each of  $X^1$ ,  $X^2$ ,  $X^3$ , and  $X^4$  is  $\text{CHR}^4$  and p is 0 or 1, then at least one  $R^4$  is other than hydrogen;
- b) when each of  $X^1$ ,  $X^2$ ,  $X^3$ , and  $X^4$  is  $\text{CHR}^4$  and Ring A is a substituted or unsubstituted piperizinyl group, then at least one  $R^4$  is other than hydrogen;
- c) when each of  $X^1$ ,  $X^2$ ,  $X^3$ , and  $X^4$  is  $\text{CHR}^4$ ,  $R^1$  is hydrogen, and  $R^2$  is 1H-indazol-3-yl, 7-fluoro-1H-indazol-3-yl, 5-fluoro-1H-indazol-3-yl, 5,7-difluoro-1H-indazol-3-yl or 5-methyl-1H-pyrazolyl, and Ring A is an unsubstituted phenyl group or is a phenyl group substituted in the ortho position with Cl or  $\text{CF}_3$ , then at least one  $R^4$  is other than hydrogen; and
- d) 5(6H)-quinazolinone, 4-anilino-7,8-dihydro-2,7-diphenyl- and 5(6H)-quinazolinone, 4-anilino-7,8-dihydro-7,7-dimethyl-2-phenyl- are excluded.

**[0030]** 2. *Compounds and Definitions:*

**[0031]** Compounds of this invention include those described generally above, and are further illustrated by the classes, subclasses, and species disclosed herein. As used herein, the following definitions shall apply unless otherwise indicated. For purposes of this invention, the chemical



elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75<sup>th</sup> Ed. Additionally, general principles of organic chemistry are described in "Organic Chemistry", Thomas Sorrell, University Science Books, Sausalito: 1999, and "March's Advanced Organic Chemistry", 5<sup>th</sup> Ed., Ed.: Smith, M.B. and March, J., John Wiley & Sons, New York: 2001, the entire contents of which are hereby incorporated by reference.

**[0032]** As described herein, compounds of the invention may optionally be substituted with one or more substituents, such as are illustrated generally above, or as exemplified by particular classes, subclasses, and species of the invention. It will be appreciated that the phrase "optionally substituted" is used interchangeably with the phrase "substituted or unsubstituted." In general, the term "substituted", whether preceded by the term "optionally" or not, refers to the replacement of hydrogen radicals in a given structure with the radical of a specified substituent. Unless otherwise indicated, an optionally substituted group may have a substituent at each substitutable position of the group, and when more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. Combinations of substituents envisioned by this invention are preferably those that result in the formation of stable or chemically feasible compounds. The term "stable", as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and preferably their recovery, purification, and use for one or more of the purposes disclosed herein. In some embodiments, a stable compound or chemically feasible compound is one that is not substantially altered when kept at a temperature of 40°C or less, in the absence of moisture or other chemically reactive conditions, for at least a week.

**[0033]** The term "aliphatic" or "aliphatic group", as used herein, means a straight-chain (i.e., unbranched) or branched, substituted or unsubstituted hydrocarbon chain that is completely saturated or that contains one or more units of unsaturation, or a monocyclic hydrocarbon or bicyclic hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic (also referred to herein as "carbocycle" "cycloaliphatic" or "cycloalkyl"), that has a single point of attachment to the rest of the molecule. Unless otherwise specified, aliphatic groups contain 1-20 aliphatic carbon atoms. In some embodiments, aliphatic groups contain 1-10 aliphatic carbon atoms. In other embodiments,

aliphatic groups contain 1-8 aliphatic carbon atoms. In still other embodiments, aliphatic groups contain 1-6 aliphatic carbon atoms, and in yet other embodiments aliphatic groups contain 1-4 aliphatic carbon atoms. In some embodiments, "cycloaliphatic" (or "carbocycle" or "cycloalkyl") refers to a monocyclic C<sub>3</sub>-C<sub>8</sub> hydrocarbon or bicyclic C<sub>8</sub>-C<sub>12</sub> hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic, that has a single point of attachment to the rest of the molecule wherein any individual ring in said bicyclic ring system has 3-7 members. Suitable aliphatic groups include, but are not limited to, linear or branched, substituted or unsubstituted alkyl, alkenyl, alkynyl groups and hybrids thereof such as (cycloalkyl)alkyl, (cycloalkenyl)alkyl or (cycloalkyl)alkenyl.

**[0034]** The term "heteroaliphatic", as used herein, means aliphatic groups wherein one or two carbon atoms are independently replaced by one or more of oxygen, sulfur, nitrogen, phosphorus, or silicon. Heteroaliphatic groups may be substituted or unsubstituted, branched or unbranched, cyclic or acyclic, and include "heterocycle", "heterocyclyl", "heterocycloaliphatic", or "heterocyclic" groups.

**[0035]** The term "heterocycle", "heterocyclyl", "heterocycloaliphatic", or "heterocyclic" as used herein means non-aromatic, monocyclic, bicyclic, or tricyclic ring systems in which one or more ring members is an independently selected heteroatom. In some embodiments, the "heterocycle", "heterocyclyl", "heterocycloaliphatic", or "heterocyclic" group has three to fourteen ring members in which one or more ring members is a heteroatom independently selected from oxygen, sulfur, nitrogen, or phosphorus, and each ring in the system contains 3 to 7 ring members.

**[0036]** The term "heteroatom" means one or more of oxygen, sulfur, nitrogen, phosphorus, or silicon (including, any oxidized form of nitrogen, sulfur, phosphorus, or silicon; the quaternized form of any basic nitrogen or; a substitutable nitrogen of a heterocyclic ring, for example N (as in 3,4-dihydro-2H-pyrrolyl), NH (as in pyrrolidinyl) or NR<sup>+</sup> (as in N-substituted pyrrolidinyl)).

**[0037]** The term "unsaturated", as used herein, means that a moiety has one or more units of unsaturation.

**[0038]** The term "alkoxy", or "thioalkyl", as used herein, refers to an alkyl group, as previously defined, attached to the principal carbon chain through an oxygen ("alkoxy") or sulfur ("thioalkyl") atom.

[0039] The terms "haloalkyl", "haloalkenyl" and "haloalkoxy" means alkyl, alkenyl or alkoxy, as the case may be, substituted with one or more halogen atoms. The term "halogen" means F, Cl, Br, or I.

[0040] The term "aryl" used alone or as part of a larger moiety as in "aralkyl", "aralkoxy", or "aryloxyalkyl", refers to monocyclic, bicyclic, and tricyclic ring systems having a total of five to fourteen ring members, wherein at least one ring in the system is aromatic and wherein each ring in the system contains 3 to 7 ring members. The term "aryl" may be used interchangeably with the term "aryl ring". The term "aryl" also refers to heteroaryl ring systems as defined hereinbelow.

[0041] The term "heteroaryl", used alone or as part of a larger moiety as in "heteroaralkyl" or "heteroaryloxy", refers to monocyclic, bicyclic, and tricyclic ring systems having a total of five to fourteen ring members, wherein at least one ring in the system is aromatic, at least one ring in the system contains one or more heteroatoms, and wherein each ring in the system contains 3 to 7 ring members. The term "heteroaryl" may be used interchangeably with the term "heteroaryl ring" or the term "heteroaromatic".

[0042] An aryl (including aralkyl, aralkoxy, aryloxyalkyl and the like) or heteroaryl (including heteroaralkyl and heteroaryloxy and the like) group may contain one or more substituents. Suitable substituents on the unsaturated carbon atom of an aryl or heteroaryl group are selected from halogen;  $-R^o$ ;  $-OR^o$ ;  $-SR^o$ ; 1,2-methylene-dioxy; 1,2-ethylenedioxy; phenyl (Ph) optionally substituted with  $R^o$ ;  $-O(Ph)$  optionally substituted with  $R^o$ ;  $-(CH_2)_{1-2}(Ph)$ , optionally substituted with  $R^o$ ;  $-CH=CH(Ph)$ , optionally substituted with  $R^o$ ;  $-NO_2$ ;  $-CN$ ;  $-N(R^o)_2$ ;  $-NR^oC(O)R^o$ ;  $-NR^oC(O)N(R^o)_2$ ;  $-NR^oCO_2R^o$ ;  $-NR^oNR^oC(O)R^o$ ;  $-NR^oNR^oC(O)N(R^o)_2$ ;  $-NR^oNR^oCO_2R^o$ ;  $-C(O)C(O)R^o$ ;  $-C(O)CH_2C(O)R^o$ ;  $-CO_2R^o$ ;  $-C(O)R^o$ ;  $-C(O)N(R^o)_2$ ;  $-OC(O)N(R^o)_2$ ;  $-S(O)_2R^o$ ;  $-SO_2N(R^o)_2$ ;  $-S(O)R^o$ ;  $-NR^oSO_2N(R^o)_2$ ;  $-NR^oSO_2R^o$ ;  $-C(=S)N(R^o)_2$ ;  $-C(=NH)-N(R^o)_2$ ; or  $-(CH_2)_{0-2}NHC(O)R^o$  wherein each independent occurrence of  $R^o$  is selected from hydrogen, optionally substituted  $C_{1-6}$  aliphatic, an unsubstituted 5-6 membered heteroaryl or heterocyclic ring, phenyl,  $-O(Ph)$ , or  $-CH_2(Ph)$ , or, notwithstanding the definition above, two independent occurrences of  $R^o$ , on the same substituent or different substituents, taken together with the atom(s) to which each  $R^o$  group is bound, form a 3-8-membered cycloalkyl, heterocyclyl, aryl, or heteroaryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Optional substituents on the aliphatic group of  $R^o$  are selected from

NH<sub>2</sub>, NH(C<sub>1-4</sub>aliphatic), N(C<sub>1-4</sub>aliphatic)<sub>2</sub>, halogen, C<sub>1-4</sub>aliphatic, OH, O(C<sub>1-4</sub>aliphatic), NO<sub>2</sub>, CN, CO<sub>2</sub>H, CO<sub>2</sub>(C<sub>1-4</sub>aliphatic), O(haloC<sub>1-4</sub> aliphatic), or haloC<sub>1-4</sub>aliphatic, wherein each of the foregoing C<sub>1-4</sub> aliphatic groups of R<sup>o</sup> is unsubstituted.

[0043] An aliphatic or heteroaliphatic group, or a non-aromatic heterocyclic ring may contain one or more substituents. Suitable substituents on the saturated carbon of an aliphatic or heteroaliphatic group, or of a non-aromatic heterocyclic ring are selected from those listed above for the unsaturated carbon of an aryl or heteroaryl group and additionally include the following: =O, =S, =NNHR<sup>\*</sup>, =NN(R<sup>\*</sup>)<sub>2</sub>, =NNHC(O)R<sup>\*</sup>, =NNHCO<sub>2</sub>(alkyl), =NNHSO<sub>2</sub>(alkyl), or =NR<sup>\*</sup>, where each R<sup>\*</sup> is independently selected from hydrogen or an optionally substituted C<sub>1-6</sub> aliphatic. Optional substituents on the aliphatic group of R<sup>\*</sup> are selected from NH<sub>2</sub>, NH(C<sub>1-4</sub> aliphatic), N(C<sub>1-4</sub> aliphatic)<sub>2</sub>, halogen, C<sub>1-4</sub> aliphatic, OH, O(C<sub>1-4</sub> aliphatic), NO<sub>2</sub>, CN, CO<sub>2</sub>H, CO<sub>2</sub>(C<sub>1-4</sub> aliphatic), O(halo C<sub>1-4</sub> aliphatic), or halo(C<sub>1-4</sub> aliphatic), wherein each of the foregoing C<sub>1-4</sub> aliphatic groups of R<sup>\*</sup> is unsubstituted.

[0044] Optional substituents on the nitrogen of a non-aromatic heterocyclic ring are selected from -R<sup>+</sup>, -N(R<sup>+</sup>)<sub>2</sub>, -C(O)R<sup>+</sup>, -CO<sub>2</sub>R<sup>+</sup>, -C(O)C(O)R<sup>+</sup>, -C(O)CH<sub>2</sub>C(O)R<sup>+</sup>, -SO<sub>2</sub>R<sup>+</sup>, -SO<sub>2</sub>N(R<sup>+</sup>)<sub>2</sub>, -C(=S)N(R<sup>+</sup>)<sub>2</sub>, -C(=NH)-N(R<sup>+</sup>)<sub>2</sub>, or -NR<sup>+</sup>SO<sub>2</sub>R<sup>+</sup>; wherein R<sup>+</sup> is hydrogen, an optionally substituted C<sub>1-6</sub> aliphatic, optionally substituted phenyl, optionally substituted -O(Ph), optionally substituted -CH<sub>2</sub>(Ph), optionally substituted -(CH<sub>2</sub>)<sub>1-2</sub>(Ph); optionally substituted -CH=CH(Ph); or an unsubstituted 5-6 membered heteroaryl or heterocyclic ring having one to four heteroatoms independently selected from oxygen, nitrogen, or sulfur, or, notwithstanding the definition above, two independent occurrences of R<sup>+</sup>, on the same substituent or different substituents, taken together with the atom(s) to which each R<sup>+</sup> group is bound, form a 3-8-membered cycloalkyl, heterocyclyl, aryl, or heteroaryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Optional substituents on the aliphatic group or the phenyl ring of R<sup>+</sup> are selected from NH<sub>2</sub>, NH(C<sub>1-4</sub> aliphatic), N(C<sub>1-4</sub> aliphatic)<sub>2</sub>, halogen, C<sub>1-4</sub> aliphatic, OH, O(C<sub>1-4</sub> aliphatic), NO<sub>2</sub>, CN, CO<sub>2</sub>H, CO<sub>2</sub>(C<sub>1-4</sub> aliphatic), O(halo C<sub>1-4</sub> aliphatic), or halo(C<sub>1-4</sub> aliphatic), wherein each of the foregoing C<sub>1-4</sub> aliphatic groups of R<sup>+</sup> is unsubstituted.

[0045] The term "alkylidene chain" refers to a straight or branched carbon chain that may be fully saturated or have one or more units of unsaturation and has two points of attachment to the rest of the molecule.

[0046] As detailed above, in some embodiments, two independent occurrences of  $R^o$  (or  $R^+$ , or any other variable similarly defined herein), are taken together together with the atom(s) to which each variable is bound to form a 3-8-membered cycloalkyl, heterocyclyl, aryl, or heteroaryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Exemplary rings that are formed when two independent occurrences of  $R^o$  (or  $R^+$ , or any other variable similarly defined herein) are taken together with the atom(s) to which each variable is bound include, but are not limited to the following: a) two independent occurrences of  $R^o$  (or  $R^+$ , or any other variable similarly defined herein) that are bound to the same atom and are taken together with that atom to form a ring, for example,  $N(R^o)_2$ , where both occurrences of  $R^o$  are taken together with the nitrogen atom to form a piperidin-1-yl, piperazin-1-yl, or morpholin-4-yl group; and b) two independent occurrences of  $R^o$  (or  $R^+$ , or any other variable similarly defined herein) that are bound to different atoms and are taken together with both of those atoms to form a ring, for example where a phenyl group is substituted with two occurrences of  $OR^o$



, these two occurrences of  $R^o$  are taken together with the oxygen atoms to which they are bound to form a fused 6-membered oxygen containing ring:



It will be appreciated that a variety of other rings can be formed when two independent occurrences of  $R^o$  (or  $R^+$ , or any other variable similarly defined herein) are taken together with the atom(s) to which each variable is bound and that the examples detailed above are not intended to be limiting.

[0047] Unless otherwise stated, structures depicted herein are also meant to include all isomeric (e.g., enantiomeric, diastereomeric, and geometric (or conformational)) forms of the structure; for example, the R and S configurations for each asymmetric center, (Z) and (E) double bond isomers, and (Z) and (E) conformational isomers. Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric, and geometric (or conformational) mixtures of the present compounds are within the scope of the invention. Unless otherwise stated, all tautomeric forms of the compounds of the invention are within the scope of the invention. Additionally, unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For

example, compounds having the present structures except for the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a  $^{13}\text{C}$ - or  $^{14}\text{C}$ -enriched carbon are within the scope of this invention. Such compounds are useful, for example, as analytical tools or probes in biological assays.

**[0048]** 3. *Description of Exemplary Compounds:*

**[0049]** In certain embodiments, the present invention provides a compound wherein p is 0 or 1. In certain other embodiments, p is 0. Or, p is 1. Or, in certain embodiments, p is 2.

**[0050]** In other embodiments, the present invention provides a compound wherein Ring A is a 5-6 membered aryl ring having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, optionally substituted at one or more carbon atoms with 0-5 occurrences of  $-\text{R}^7$ , and at one or more substitutable nitrogen atoms with  $-\text{R}^8$ , wherein  $\text{R}^7$  and  $\text{R}^8$  are as defined above.

**[0051]** In one embodiment of formula I,  $\text{X}^1$ ,  $\text{X}^2$ , and  $\text{X}^4$  are  $\text{CH}_2$ , and  $\text{X}^3$  is  $\text{CH-Me}$  or  $\text{N-(C}_{1-4}\text{ alkyl)}$ ,  $\text{N-benzyl}$ , p is 0, 1 or 2,  $\text{R}^1$  is methyl and  $\text{R}^2$  is furan-2-ylmethyl, dimethylaminoethyl, or methyl, or  $\text{R}^1$  and  $\text{R}^2$  taken together form piperidiny, piperaziny, 4-methylpiperidiny, 4- $\text{C}_{1-4}$  alkoxy piperidiny, morpholiny, 4-carboxy- $\text{C}_{1-4}$ alkylpiperaziny, or 4- $\text{C}_{1-4}$  alkylsulfonylpiperaziny, and ring A is 2-hydroxyphenyl, 2-hydroxy-6-fluorophenyl, phenyl-2-disodium phosphate, or pyrrolyl.

**[0052]** In one embodiment of formula I,  $\text{X}^1$ ,  $\text{X}^2$ , and  $\text{X}^4$  are  $\text{CH}_2$ , and  $\text{X}^3$  is  $\text{CH-Me}$  or  $\text{N-Me}$ , p is 1,  $\text{R}^1$  is methyl and  $\text{R}^2$  is furan-2-ylmethyl or methyl, or  $\text{R}^1$  and  $\text{R}^2$  taken together form piperidiny, 4-methylpiperidiny, morpholiny, or 4- $\text{C}_{1-4}$  alkylsulfonylpiperaziny, and ring A is 2-hydroxyphenyl or 2-hydroxy-6-fluorophenyl.

**[0053]** In one embodiment of formula I,  $\text{X}^1$ ,  $\text{X}^2$ , and  $\text{X}^4$  are  $\text{CH}_2$ , and  $\text{X}^3$  is  $\text{CH-Me}$ , p is 1,  $\text{R}^1$  is methyl and  $\text{R}^2$  is furan-2-ylmethyl or methyl, or  $\text{R}^1$  and  $\text{R}^2$  taken together form piperidiny, 4-methylpiperidiny, or 4- $\text{C}_{1-4}$  alkylsulfonylpiperaziny, and ring A is 2-hydroxyphenyl or 2-hydroxy-6-fluorophenyl.

**[0054]** In one embodiment of formula I,  $\text{X}^1$ ,  $\text{X}^2$ , and  $\text{X}^4$  are  $\text{CH}_2$ , and  $\text{X}^3$  is  $\text{CH-Me}$ , p is 1,  $\text{R}^1$  and  $\text{R}^2$  taken together form 4-methylpiperidiny or 4- $\text{C}_{1-4}$  alkylsulfonylpiperaziny, and ring A is 2-hydroxy or 2-hydroxy-6-fluorophenyl.

**[0055]** In one embodiment of formula I,  $X^1$ , and  $X^2$  are  $CH_2$ ,  $X^4$  is  $CHOH$  or  $CH_2$ , and  $X^3$  is  $CH_2$ ,  $CH-Me$ , or  $C(O)-Me$ ,  $p$  is 1,  $R^1$  is methyl and  $R^2$  methyl or methylaminoethyl, or  $R^1$  and  $R^2$  taken together form 1-piperidinyl, 1-piperazinyl, or 4-methylpiperazinyl, and ring A is 2-hydroxyphenyl, 2-fluorophenyl, or 1-pyrrolyl.

**[0056]** In one embodiment of formula I,  $X^1$ ,  $X^2$ , and  $X^4$  are  $CH_2$ , and  $X^3$  is  $CH_2$  or  $CH-Me$ ,  $p$  is 1,  $R^1$  is methyl and  $R^2$  methyl or methylaminoethyl, or  $R^1$  and  $R^2$  taken together form 1-piperazinyl or 4-methylpiperazinyl, and ring A is 2-hydroxyphenyl or 1-pyrrolyl.

**[0057]** In one embodiment of formula I,  $X^1$  and  $X^4$  are  $CH_2$ ,  $X^2$  is  $CH_2$ ,  $CHMe$ , or  $C(O)OMe$ , and  $X^3$  is N-benzyl, N-(3-methoxybenzyl), N-(4-carboxymethylbenzyl),  $CH_2$ , or  $CH-Me$ ,  $p$  is 1,  $R^1$  is methyl or benzyl and  $R^2$  is methyl or dimethylaminoethyl, or  $R^1$  and  $R^2$  taken together form a 1-piperazinyl, 1-piperidinyl, 4-carboxyethylpiperazinyl, 4- $C_{1-4}$  alkylsulfonyl piperazinyl, 4-methylpiperidinyl, 4-methoxypiperidinyl, 4-methylpiperazinyl, 3-diethylaminocarbonylpiperidinyl, or morpholinyl, and ring A is 2-hydroxyphenyl, 2-methoxyphenyl, or 1-pyrrolyl.

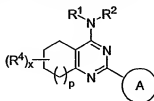
**[0058]** In one embodiment of formula I,  $X^1$ ,  $X^2$ , and  $X^4$  are  $CH_2$ , and  $X^3$  is N-benzyl, N-(3-methoxybenzyl), N-(4-carboxymethylbenzyl),  $CH_2$ , or  $CH-Me$ ,  $p$  is 1,  $R^1$  is methyl or benzyl and  $R^2$  is methyl or dimethylaminoethyl, or  $R^1$  and  $R^2$  taken together form a 1-piperazinyl, 1-piperidinyl, 4-carboxyethylpiperazinyl, 4- $C_{1-4}$  alkylsulfonyl piperazinyl, 4-methylpiperidinyl, 4-methoxypiperidinyl, 3-diethylaminocarbonylpiperidinyl, or morpholinyl, and ring A is 2-hydroxyphenyl, 2-methoxyphenyl, or 1-pyrrolyl.

**[0059]** In one embodiment of formula I,  $X^1$ ,  $X^2$ , and  $X^4$  are  $CH_2$ , and  $X^3$  is N-benzyl, N-(3-methoxybenzyl), N-(4-carboxymethylbenzyl), or  $CH-Me$ ,  $p$  is 1,  $R^1$  is methyl or benzyl and  $R^2$  is methyl or dimethylaminoethyl, or  $R^1$  and  $R^2$  taken together form a 4- $C_{1-4}$  alkylsulfonyl piperazinyl, 4-methylpiperidinyl, or 3-diethylaminocarbonylpiperidinyl, and ring A is 2-hydroxyphenyl or 2-methoxyphenyl.

**[0060]** In one embodiment of formula I,  $X^1$ ,  $X^2$ , and  $X^4$  are  $CH_2$ , and  $X^3$  is N-(3-methoxybenzyl) or  $CH-Me$ ,  $p$  is 1,  $R^1$  and  $R^2$  are both methyl, or  $R^1$  and  $R^2$  taken together form a 4-methylsulfonylpiperazinyl or 4-ethylsulfonylpiperazinyl, and ring A is 2-hydroxyphenyl or 2-methoxyphenyl.

[0061] In one embodiment of formula I,  $X^1$ ,  $X^2$ , and  $X^4$  are  $CH_2$ , and  $X^3$  is  $CH_2$  or  $CH-Me$ ,  $p$  is 1,  $R^1$  and  $R^2$  each are methyl or  $R^1$  and  $R^2$  taken together form 1-piperazinyl, and ring A is 2-hydroxyphenyl or 1-pyrrolyl.

[0062] In certain embodiments, the present invention provides a compound of formula I':



I'

or a pharmaceutically acceptable salt thereof, wherein:

$R^1$  and  $R^2$  are each independently hydrogen, or an optionally substituted group selected from  $C_{1-6}$  aliphatic, a 5-6 membered aryl ring having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or  $R^1$  and  $R^2$ , taken together with the nitrogen atom to which they are bound, form an optionally substituted 3-8 membered heterocyclyl or heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein  $R^1$ ,  $R^2$ , or any ring formed by  $R^1$  and  $R^2$  taken together, are each independently optionally substituted at one or more carbon atoms with 0-4 occurrences of  $-R^5$ , and at one or more substitutable nitrogen atoms with  $-R^6$ ;

Ring A is a 5-6 membered monocyclic or 8-10 membered bicyclic aryl ring having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, optionally substituted at one or more carbon atoms with 0-5 occurrences of  $-R^7$ , and at one or more substitutable nitrogen atoms with  $-R^8$ ;

$x$  is 0-6;

$p$  is 0, 1, or 2; and

each occurrence of  $R^4$ ,  $R^5$ , and  $R^7$  is independently  $Q-R^X$ , wherein  $Q$  is a bond or is a  $C_1-C_6$  alkylidene chain wherein up to two non-adjacent methylene units of  $Q$  are optionally and independently replaced by  $CO$ ,  $CO_2$ ,  $COCO$ ,  $CONR$ ,  $OCONR$ ,  $NRNR$ ,  $NRNR$ CO,  $NR$ CO,  $NR$ CO<sub>2</sub>,  $NR$ CONR,  $SO$ ,  $SO_2$ ,  $NRSO_2$ ,  $SO_2NR$ ,  $NRSO_2NR$ ,  $O$ ,  $S$ , or  $NR$ ;



each occurrence of R is independently selected from hydrogen or an optionally substituted  $C_{1-6}$  aliphatic group;

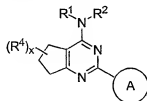
each occurrence of R' is independently selected from hydrogen or an optionally substituted group selected from  $C_{1-8}$  aliphatic,  $C_{6-10}$  aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclyl ring having 3-10 ring atoms, or wherein R and R' taken together with the atom(s) to which they are bound, or two occurrences of R' taken together with the atom(s) to which they are bound, form a 5-8 membered cycloalkyl, heterocyclyl, aryl, or heteroaryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and

each occurrence of  $R^6$  or  $R^8$  is independently R', -COR', -CO<sub>2</sub>( $C_{1-6}$  aliphatic), -CON(R')<sub>2</sub>, or -SO<sub>2</sub>R'.

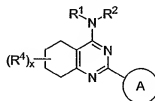
[0063] In certain other embodiments, for compounds of formula I' describe generally above and herein:

- a) when p is 0 or 1, then at least one  $R^4$  is other than hydrogen;
- b) when Ring A is a substituted or unsubstituted piperizinyl group, then at least one  $R^4$  is other than hydrogen;
- c) when R<sup>1</sup> is hydrogen and R<sup>2</sup> is 1H-indazol-3-yl, 7-fluoro-1H-indazol-3-yl, 5-fluoro-1H-indazol-3-yl, 5,7-difluoro-1H-indazol-3-yl or 5-methyl-1H-pyrazolyl, and Ring A is an unsubstituted phenyl group or is a phenyl group substituted in the ortho position with Cl or CF<sub>3</sub>, then at least one  $R^4$  is other than hydrogen; and
- d) 5(6H)-quinazolinone, 4-anilino-7,8-dihydro-2,7-diphenyl- and 5(6H)-quinazolinone, 4-anilino-7,8-dihydro-7,7-dimethyl-2-phenyl- are excluded.

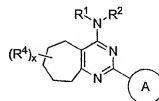
[0064] As described generally above for compounds of formula I', p is 0, 1, or 2, and thus compounds have the structure shown in formula I-A, I-B, or I-C:



I-A



I-B



I-C

[0065] In certain preferred embodiments of formula I', p is 1 and compounds have the structure as shown in I-B.

[0066] In one embodiment of formula I-B:

(i) ring A is pyrrolyl, pyridyl, fluorophenyl, hydroxyphenyl, acyloxyphenyl, hydroxy-fluorophenyl, methoxyphenyl, phenyl-phosphate disodium salt, methylpiperidyl, ethyl-carbamic acid phenyl ester;

(ii) x is 0-2, and R<sup>4</sup> is C<sub>1-4</sub> alkyl optionally substituted with hydroxy, C<sub>1-4</sub> alkoxy, or halo, hydroxy, C<sub>1-4</sub> alkylcarbonyloxy or carbo(C<sub>1-4</sub>alkoxy);

(iii) R<sup>1</sup> is hydrogen, C<sub>1-4</sub> alkyl, or benzyl, and R<sup>2</sup> is C<sub>1-4</sub> alkyl, di(C<sub>1-4</sub> alkyl)amino-C<sub>1-4</sub> alkyl, 2-(2'-tetrahydrofuranyl)methyl, 2-hydroxy-1-methyl-ethyl, or imidazol-5-yl-ethyl, or

(iii) R<sup>1</sup> and R<sup>2</sup> taken together form a ring selected from N-pyrrolidinyl, N-piperidinyl, N-piperazinyl, morpholinyl, thiomorpholinyl, (C<sub>1-4</sub> alkyl)sulfonylpiperazinyl, wherein said ring is optionally substituted with up to 3 substituents selected from halo, oxo, hydroxy, trifluoromethyl, -O- C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkyl optionally substituted with hydroxy, amino, aminocarbonyl, di(C<sub>1-4</sub>alkyl)aminocarbonyl, or carboxy.

[0067] In one embodiment of formula I-B:

(i) ring A is 1-pyrrolyl, 2-pyridyl, 2-fluorophenyl, 2-hydroxyphenyl, 2-acyloxyphenyl, 2-hydroxy-6-fluorophenyl, 2-methoxyphenyl, phenyl-2-phosphate disodium salt, or 4-methylpiperidyl, 2-ethyl-carbamic acid phenyl ester

(ii) x is 0, or x is 1 and R<sup>4</sup> is 6-methyl, 7-methyl, 8-hydroxy, or 2-t-butylcarbonyloxy, or x is 2, and R<sup>4</sup> is 6-carboxymethyl and 7-carboxymethyl;

(iii) R<sup>1</sup> is hydrogen, methyl, ethyl, or benzyl, and R<sup>2</sup> is methyl, ethyl, dimethylaminoethyl, 2-(2'-tetrahydrofuranyl)methyl, 2-hydroxy-1-methyl-ethyl, methylaminoethyl, imidazol-5-yl-ethyl, or

(iii) R<sup>1</sup> and R<sup>2</sup> taken together form 4-methoxypiperidinyl, N-pyrrolidinyl, 3-trifluoromethyl-1-pyrrolidinyl, 4-butylsulfonyl-piperazinyl, 1-piperidinyl, 1-piperazinyl, 4-methylpiperidinyl, 4-hydroxypiperidinyl, 4-morpholinyl, 4-methylsulfonylpiperazinyl, 4-ethylsulfonylpiperazinyl, 4-isopropylsulfonylpiperazinyl, N-piperidinyl, 3-diethylaminocarbonyl-1-piperidinyl, 4-oxo-piperidinyl, 3-aminocarbonyl-piperidinyl, 4-methylpiperazinyl, or 4-carboxyethyl-piperazinyl.

[0068] In one embodiment of formula I-B, ring A is 2-pyridyl, 2-fluorophenyl, 2-hydroxyphenyl, 2-acyloxyphenyl, 2-hydroxy-6-fluorophenyl, 2-methoxyphenyl, or 4-methylpiperidyl, x is 0, or x is 1 and R<sup>4</sup> is 6-methyl, 7-methyl, or 8-hydroxy, R<sup>1</sup> is methyl, ethyl, or benzyl, and R<sup>2</sup> is methyl, ethyl, dimethylaminoethyl, or 2-(2'-tetrahydrofuranyl)methyl, or R<sup>1</sup>

and R<sup>2</sup> taken together form 4-methoxypiperidinyl, N-pyrrolidinyl, 4-butylsulfonyl-piperazinyl, piperidinyl, 4-methylpiperidinyl, 4-hydroxypiperidinyl, 4-morpholinyl, 4-methylsulfonylpiperazinyl, 4-ethylsulfonylpiperazinyl, N-piperidinyl, 3-diethylaminocarbonyl-1-piperidinyl, or 4-carboxyethyl-piperazinyl

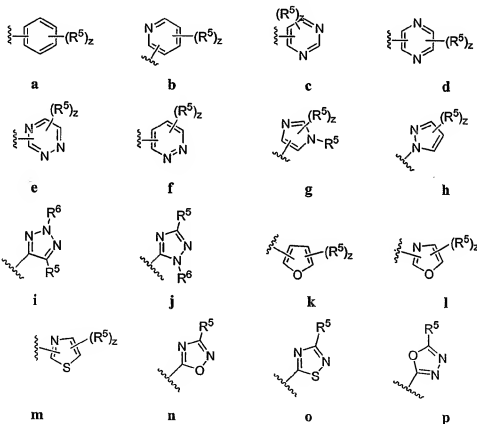
[0069] In one embodiment of formula I-B, ring A is 2-pyridyl, 2-hydroxyphenyl, 2-acyloxyphenyl, 2-hydroxy-6-fluorophenyl, or 4-methylpiperidyl, x is 0, or x is 1 and R<sup>4</sup> is 7-methyl, R<sup>1</sup> is methyl and R<sup>2</sup> is methyl or 2-(2'-tetrahydrofuranyl)methyl, or R<sup>1</sup> and R<sup>2</sup> taken together form 4-butylsulfonyl-piperazinyl, piperidinyl, 4-methylpiperidinyl, 4-morpholinyl, 4-methylsulfonylpiperazinyl, 4-ethylsulfonylpiperazinyl, 4-piperidinyl, or 4-carboxyethyl-piperazinyl.

[0070] In one embodiment of formula I-B, ring A is 2-hydroxyphenyl, R<sup>1</sup> and R<sup>2</sup>, taken together, form a 1-piperidinyl ring, x is 1, and R<sup>4</sup> is 7-methyl.

[0071] In certain preferred embodiments of any of formulae I', I-A, I-B, and I-C, neither R<sup>1</sup> nor R<sup>2</sup> is hydrogen, and R<sup>1</sup> and R<sup>2</sup> are each independently selected from a 5- or 6-membered aryl ring having 0-5 heteroatoms independently selected from N, O, or S, a 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from N, O, or S, or an optionally substituted C<sub>1-4</sub> aliphatic group, wherein one or more methylene units in the C<sub>1-4</sub> aliphatic group are optionally and independently replaced with NR, O, (CO)O, O(CO), NR(CO), (CO)NR, SO<sub>2</sub>(NR), or (NR)SO<sub>2</sub>. In more preferred embodiments of any of formulae I', I-A, I-B, and I-C, both R<sup>1</sup> and R<sup>2</sup> are each independently an optionally substituted C<sub>1-4</sub> aliphatic group, wherein one or more methylene units in the C<sub>1-4</sub> aliphatic group are optionally and independently replaced with NR, O, (CO)O, O(CO), NR(CO), (CO)NR, SO<sub>2</sub>(NR), or (NR)SO<sub>2</sub>. In yet other preferred embodiments of any of formulae I', I-A, I-B, and I-C, when R<sup>1</sup> and R<sup>2</sup> are each independently an optionally substituted C<sub>1-4</sub> aliphatic group, wherein one or more methylene units in the C<sub>1-4</sub> aliphatic group are optionally and independently replaced with NR, O, (CO)O, O(CO), NR(CO), (CO)NR, SO<sub>2</sub>(NR), or (NR)SO<sub>2</sub>, preferred R<sup>1</sup> and R<sup>2</sup> groups are each independently optionally substituted methyl, ethyl, cyclopropyl, n-propyl, propenyl, cyclobutyl, (CO)OCH<sub>2</sub>CH<sub>3</sub>, (CH<sub>2</sub>)<sub>2</sub>OCH<sub>3</sub>, CH<sub>2</sub>(CO)OCH<sub>2</sub>CH<sub>3</sub>, CH<sub>2</sub>(CO)OCH<sub>3</sub>, CH(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>3</sub>, or t-butyl, or n-butyl. Most preferred R<sup>1</sup> and R<sup>2</sup> groups of any of formulae I', I-A, I-B, and I-C include those shown below in Table 2.

[0072] In other preferred embodiments of any of formulae I', I-A, I-B, and I-C, one of  $R^1$  or  $R^2$  is hydrogen and the other of  $R^1$  or  $R^2$  is a 5-6 membered aryl ring having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In other embodiments, one of  $R^1$  or  $R^2$  is hydrogen, and the other of  $R^1$  or  $R^2$  is an optionally substituted  $C_{1-4}$  aliphatic group, wherein one or more methylene units in the  $C_{1-4}$  aliphatic group are optionally and independently replaced with NR, O, (CO)O, O(CO), NR(CO), (CO)NR,  $SO_2$ (NR), or (NR) $SO_2$ .

[0073] For those embodiments described above and herein where  $R^1$  or  $R^2$  is a 5- or 6-membered aryl ring having 0-5 heteroatoms independently selected from N, O, or S, or a 3-7 membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from N, O, or S, preferred  $R^1$  and  $R^2$  groups are selected from:



**q****r****s****t****u****v****w****x****y****z****aa****bb**

wherein each  $R^5$  and  $R^6$  are as previously defined and each  $z$  is independently 0-4. Most preferred rings include those shown below in Table 2.

[0074] In still other embodiments, for compounds of any of formulae I', I-A, I-B, and I-C,  $R^1$  and  $R^2$ , taken together with the nitrogen atom to which they are bound, form an optionally substituted 3-8 membered heterocyclyl ring having 1-3 heteroatoms independently selected from nitrogen or oxygen. In certain preferred embodiments of any of formulae I', I-A, I-B, and I-C,  $R^1$  and  $R^2$  are taken together with the nitrogen atom to which they are bound and form a 3-8 membered heterocyclyl group selected from:

**cc****dd****ee****ff****gg****hh**

wherein each  $R^5$  and  $R^6$  are as previously defined and each  $z$  is independently 0-4.

[0075] In other preferred embodiments, for compounds of any of formulae **I'**, **I-A**, **I-B**, and **I-C**,  $R^1$  and  $R^2$  taken together are optionally substituted pyrrolidin-1-yl (**ff**), piperidin-1-yl (**dd**), piperazin-1-yl (**ee**), or morpholin-4-yl (**ee**).

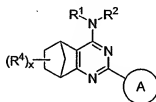
[0076] In preferred embodiments of any of formulae **I'**, **I-A**, **I-B**, and **I-C**,  $z$  is 0-2. In other preferred embodiments of any of formulae **I'**, **I-A**, **I-B**, and **I-C**,  $z$  is 0 and the ring is unsubstituted.

[0077] Preferred  $R^5$  groups of any of formulae **I'**, **I-A**, **I-B**, and **I-C**, when present, are independently halogen, CN,  $NO_2$ , or an optionally substituted group selected from  $C_{1-6}$  alkyl, aryl,  $aryl(C_{1-6})alkyl$ ,  $-N(R')_2$ ,  $-CH_2N(R')_2$ ,  $OR'$ ,  $-CH_2OR'$ ,  $SR'$ ,  $-CH_2SR'$ ,  $COOR'$ ,  $-NRCOR'$ ,  $-(CH_2)_2N(R')_2$ ,  $-(CH_2)_2OR'$ ,  $-(CH_2)_2SR'$ ,  $-COR'$ ,  $-CON(R')_2$ , or  $-S(O)_2N(R')_2$ . In more preferred embodiments of any of formulae **I'**, **I-A**, **I-B**, and **I-C**,  $R^5$  groups are each independently Cl, Br, F,  $CF_3$ , Me, Et, CN,  $NO_2$ ,  $-COOH$ ,  $NH_2$ ,  $-N(CH_3)_2$ ,  $-N(Et)_2$ ,  $-N(iPr)_2$ ,  $-O(CH_2)_2OCH_3$ ,  $-CONH_2$ ,  $-COOCH_3$ ,  $-OH$ ,  $-CH_2OH$ ,  $-NHCOCH_3$ ,  $-SO_2NH_2$ ,  $SO_2N(CH_3)_2$ , piperidinyl, piperiziny, morpholino, or an optionally substituted group selected from  $C_{1-4}$  alkoxy, phenyl, phenyloxy, benzyl, or benzyloxy. Most preferred  $R^5$  groups include those shown below in Table 2.

[0078] In preferred embodiments of any of formulae **I'**, **I-A**, **I-B**, and **I-C**,  $R^6$  groups are independently hydrogen, or an optionally substituted group selected from  $C_{1-6}$  alkyl, aryl,  $aryl(C_{1-6})alkyl$ ,  $-N(R')_2$ ,  $-CH_2N(R')_2$ ,  $-CH_2OR'$ ,  $-CH_2SR'$ ,  $-(CH_2)_2N(R')_2$ ,  $-(CH_2)_2OR'$ ,  $-(CH_2)_2SR'$ ,  $-COR'$ ,  $-CON(R')_2$ , or  $-S(O)_2N(R')_2$ . In more preferred embodiments of any of formulae **I'**, **I-A**, **I-B**, and **I-C**,  $R^6$  groups are each independently H, Me,  $CF_3$ , ethyl, propyl, butyl, pentyl,  $CO(C_{1-4}alkyl)$ ,  $-CONH_2$ ,  $-COO(C_{1-4}alkyl)$ ,  $-CH_2OH$ ,  $-SO_2NH_2$ ,  $SO_2N(CH_3)_2$ , or optionally substituted phenyl. Most preferred  $R^6$  groups of any of formulae **I'**, **I-A**, **I-B**, and **I-C** include those shown below in Table 2.

[0079] In preferred embodiments of any of formulae **I'**, **I-A**, **I-B**, and **I-C**,  $x$  is 0, 1, or 2 and each  $R^4$  is independently hydrogen, halogen, CN,  $NO_2$ , or an optionally substituted group selected from  $C_{1-6}$  alkyl, aryl,  $aryl(C_{1-6})alkyl$ ,  $-N(R')_2$ ,  $-CH_2N(R')_2$ ,  $OR'$ ,  $-CH_2OR'$ ,  $SR'$ ,  $-CH_2SR'$ ,  $COOR'$ ,  $-NRCOR'$ ,  $-(CH_2)_2N(R')_2$ ,  $-(CH_2)_2OR'$ ,  $-(CH_2)_2SR'$ ,  $-COR'$ ,  $-CON(R')_2$ , or  $-S(O)_2N(R')_2$ . In more preferred embodiments of any of formulae **I'**, **I-A**, **I-B**, and **I-C**, each  $R^4$  is independently H, Cl, Br, F,  $CF_3$ , Me, Et, CN,  $NO_2$ ,  $-COOH$ ,  $NH_2$ ,  $-N(CH_3)_2$ ,  $-N(Et)_2$ ,  $-N(iPr)_2$ ,  $-O(CH_2)_2OCH_3$ ,  $-CONH_2$ ,  $-COOCH_3$ ,  $-OH$ ,  $-CH_2OH$ ,  $-NHCOCH_3$ ,  $-SO_2NH_2$ ,  $SO_2N(CH_3)_2$ ,

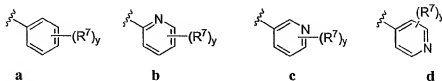
piperidinyl, piperiziny, morpholino, or an optionally substituted group selected from C<sub>1-4</sub> alkoxy, phenyl, phenoxy, benzyl, or benzyloxy. In still other preferred embodiments of any of formulae I', I-A, I-B, and I-C, two occurrences of R<sup>4</sup>, taken together form an optionally substituted 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In some preferred embodiments of any of formulae I', I-A, I-B, and I-C, two occurrences of R<sup>4</sup>, taken together form a cycloalkyl group and compounds have the structure as shown in formula I-B-i:



I-B-i

[0080] Other preferred R<sup>4</sup> groups of any of formulae I', I-A, I-B, and I-C include those shown below in Table 2.

[0081] In certain embodiments, for compounds of any of formulae I', I-A, I-B, and I-C, Ring A is a phenyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, pyrrolyl, piperidinyl, indolyl, indazolyl, benzotriazolyl, pyrazolyl, benzopyrazolyl, imidazolyl, benzimidazolyl, thiazolyl, benzthiazolyl, oxazolyl, benzoxazolyl, isoxazolyl, benzisoxazolyl, isothiazolyl, benzisothiazolyl, triazolyl, benzotriazolyl, thiadiazolyl, thienyl, benzothienyl, furanoyl, benzofuranoyl, or triazinyl ring, each optionally substituted at one or more carbon atoms with 0-5 occurrences of -R<sup>7</sup>, and at one or more substitutable nitrogen atoms with -R<sup>8</sup>. It will be appreciated that Ring A can be attached to the pyrimidinyl ring through any available carbon or nitrogen atom (e.g., a thiazole ring can be attached in the 2-, 4-, or 5-position). In certain preferred embodiments of any of formulae I', I-A, I-B, and I-C, Ring A is optionally substituted phenyl, 2-pyridyl, 3-pyridyl, or 4-pyridyl:



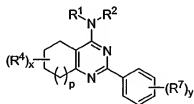
wherein each y is independently 0-5 and R<sup>7</sup> is as defined generally above and herein.

[0082] In preferred embodiments of any of formulae I', I-A, I-B, and I-C, y is 0-2. In other preferred embodiments of any of formulae I', I-A, I-B, and I-C, y is 0 and Ring A is

unsubstituted. In preferred embodiments of any of formulae **I'**, **I-A**, **I-B**, and **I-C**,  $R^7$  groups are independently hydrogen, halogen, CN,  $\text{NO}_2$ , or an optionally substituted group selected from  $\text{C}_{1-6}$  alkyl, aryl,  $\text{aryl}(\text{C}_{1-6})\text{alkyl}$ ,  $-\text{N}(\text{R}')_2$ ,  $-\text{CH}_2\text{N}(\text{R}')_2$ ,  $\text{OR}'$ ,  $-\text{CH}_2\text{OR}'$ ,  $\text{SR}'$ ,  $-\text{CH}_2\text{SR}'$ ,  $\text{COOR}'$ ,  $-\text{NRCOR}'$ ,  $-(\text{CH}_2)_2\text{N}(\text{R}')_2$ ,  $-(\text{CH}_2)_2\text{OR}'$ ,  $-(\text{CH}_2)_2\text{SR}'$ ,  $-\text{COR}'$ ,  $-\text{CON}(\text{R}')_2$ , or  $-\text{S}(\text{O})_2\text{N}(\text{R}')_2$ . In more preferred embodiments of any of formulae **I'**, **I-A**, **I-B**, and **I-C**,  $R^7$  groups are each independently H, Cl, Br, F,  $\text{CF}_3$ , Me, Et, CN,  $\text{NO}_2$ ,  $-\text{COOH}$ ,  $\text{NH}_2$ ,  $-\text{N}(\text{CH}_3)_2$ ,  $-\text{N}(\text{Et})_2$ ,  $-\text{N}(\text{iPr})_2$ ,  $-\text{O}(\text{CH}_2)_2\text{OCH}_3$ ,  $-\text{CONH}_2$ ,  $-\text{COOCH}_3$ ,  $-\text{OH}$ ,  $-\text{CH}_2\text{OH}$ ,  $-\text{NHCOCH}_3$ ,  $-\text{SO}_2\text{NH}_2$ ,  $\text{SO}_2\text{N}(\text{CH}_3)_2$ , piperidinyl, piperiziny, morpholino, or an optionally substituted group selected from  $\text{C}_{1-4}$  alkoxy, phenyl, phenyloxy, benzyl, or benzyloxy. Most preferred  $R^7$  groups of any of formulae **I'**, **I-A**, **I-B**, and **I-C**, include those shown below in Table 2.

[0083] In preferred embodiments of any of formulae **I'**, **I-A**, **I-B**, and **I-C**,  $R^8$  groups are independently hydrogen, or an optionally substituted group selected from  $\text{C}_{1-6}$  alkyl, aryl,  $\text{aryl}(\text{C}_{1-6})\text{alkyl}$ ,  $-\text{N}(\text{R}')_2$ ,  $-\text{CH}_2\text{N}(\text{R}')_2$ ,  $-\text{CH}_2\text{OR}'$ ,  $-\text{CH}_2\text{SR}'$ ,  $-(\text{CH}_2)_2\text{N}(\text{R}')_2$ ,  $-(\text{CH}_2)_2\text{OR}'$ ,  $-(\text{CH}_2)_2\text{SR}'$ ,  $-\text{COR}'$ ,  $-\text{CON}(\text{R}')_2$ , or  $-\text{S}(\text{O})_2\text{N}(\text{R}')_2$ . In more preferred embodiments of any of formulae **I'**, **I-A**, **I-B**, and **I-C**,  $R^8$  groups are each independently H, Me,  $\text{CF}_3$ , ethyl, propyl, butyl, pentyl,  $\text{CO}(\text{C}_{1-4}\text{ alkyl})$ ,  $-\text{CONH}_2$ ,  $-\text{COO}(\text{C}_{1-4}\text{ alkyl})$ ,  $-\text{CH}_2\text{OH}$ ,  $-\text{SO}_2\text{NH}_2$ ,  $\text{SO}_2\text{N}(\text{CH}_3)_2$ , or optionally substituted phenyl. Most preferred  $R^8$  groups of any of formulae **I'**, **I-A**, **I-B**, and **I-C** include those shown below in Table 2.

[0084] In another embodiment, Ring A is optionally substituted phenyl and compounds of formula **II** are provided:

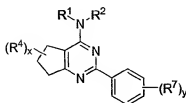


**II**

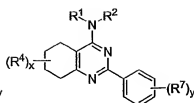
wherein  $R^1$ ,  $R^2$ ,  $R^4$ ,  $R^7$ ,  $p$ , and  $y$  are as defined generally and in subsets above and herein.

[0085] In certain other preferred embodiments, for compounds of formula **I-A**, **I-B**, or **I-C**, Ring A is phenyl and compounds have the structure shown in formula **II-A**, **II-B**, or **II-C**.

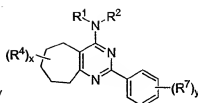




II-A



II-B

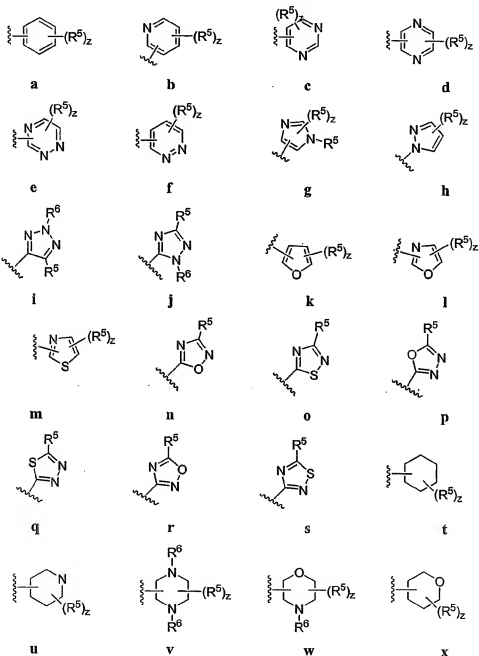


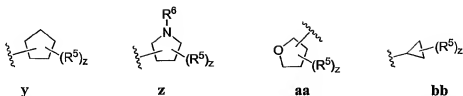
II-C

[0086] In certain preferred embodiments for compounds of any of formulae **II**, **II-A**, **II-B**, or **II-C**, neither  $R^1$  nor  $R^2$  is hydrogen, and  $R^1$  and  $R^2$  are each independently selected from a 5- or 6-membered aryl ring having 0-5 heteroatoms independently selected from N, O, or S; a 3-7 membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from N, O, or S, or an optionally substituted  $C_{1-4}$  aliphatic group, wherein one or more methylene units in the  $C_{1-4}$  aliphatic group are optionally and independently replaced with NR, O, (CO)O, O(CO), NR(CO), (CO)NR,  $SO_2$ (NR), or (NR) $SO_2$ . In more preferred embodiments of any of formulae **II**, **II-A**, **II-B**, or **II-C**, both  $R^1$  and  $R^2$  are an optionally substituted  $C_{1-4}$  aliphatic group, wherein one or more methylene units in the  $C_{1-4}$  aliphatic group are optionally and independently replaced with NR, O, (CO)O, O(CO), NR(CO), (CO)NR,  $SO_2$ (NR), or (NR) $SO_2$ . In yet other preferred embodiments of any of formulae **II**, **II-A**, **II-B**, or **II-C**, when  $R^1$  and  $R^2$  are an optionally substituted  $C_{1-4}$  aliphatic group, wherein one or more methylene units in the  $C_{1-4}$  aliphatic group are optionally and independently replaced with NR, O, (CO)O, O(CO), NR(CO), (CO)NR,  $SO_2$ (NR), or (NR) $SO_2$ , preferred  $R^1$  and  $R^2$  groups are optionally substituted methyl, ethyl, cyclopropyl, n-propyl, propenyl, cyclobutyl, (CO)OCH<sub>2</sub>CH<sub>3</sub>, (CH<sub>2</sub>)<sub>2</sub>OCH<sub>3</sub>, CH<sub>2</sub>(CO)OCH<sub>2</sub>CH<sub>3</sub>, CH<sub>2</sub>(CO)OCH<sub>3</sub>, CH(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>3</sub>, or t-butyl, or n-butyl. Most preferred  $R^1$  and  $R^2$  groups of any of formulae **II**, **II-A**, **II-B**, or **II-C** include those shown below in Table 2.

[0087] In other preferred embodiments of any of formulae **II**, **II-A**, **II-B**, or **II-C**, one of  $R^1$  or  $R^2$  is hydrogen and the other of  $R^1$  or  $R^2$  is a 5-6 membered aryl ring having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In other embodiments of any of formulae **II**, **II-A**, **II-B**, or **II-C**, one of  $R^1$  or  $R^2$  is hydrogen, and the other of  $R^1$  or  $R^2$  is an optionally substituted  $C_{1-4}$  aliphatic group, wherein one or more methylene units in the  $C_{1-4}$  aliphatic group are optionally and independently replaced with NR, O, (CO)O, O(CO), NR(CO), (CO)NR,  $SO_2$ (NR), or (NR) $SO_2$ .

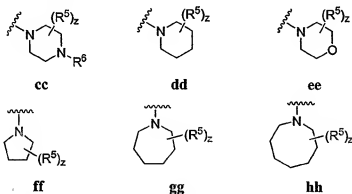
[0088] For those embodiments described above and herein where  $R^1$  or  $R^2$  is a 5- or 6-membered aryl ring having 0-5 heteroatoms independently selected from N, O, or S, or a 3-7 membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from N, O, or S, preferred  $R^1$  and  $R^2$  groups are selected from:





wherein each  $R^5$  and  $R^6$  are as previously defined and each  $z$  is independently 0-4. Most preferred rings include those shown below in Table 2.

[0089] In still other embodiments, for compounds of any of formulae **II**, **II-A**, **II-B**, or **II-C**,  $R^1$  and  $R^2$ , taken together with the nitrogen atom to which they are bound, form an optionally substituted 3-8 membered heterocyclyl ring having 1-3 heteroatoms independently selected from nitrogen or oxygen. In certain preferred embodiments of any of formulae **II**, **II-A**, **II-B**, or **II-C**,  $R^1$  and  $R^2$  are taken together with the nitrogen atom to which they are bound and form a 3-8 membered heterocyclyl group selected from:



wherein each  $R^5$  and  $R^6$  are as previously defined and each  $z$  is independently 0-4.

[0090] In other preferred embodiments, for compounds of any of formulae **II**, **II-A**, **II-B**, or **II-C**,  $R^1$  and  $R^2$  taken together are optionally substituted pyrrolidin-1-yl (**ff**), piperidin-1-yl (**dd**), piperazin-1-yl (**cc**), or morpholin-4-yl (**ee**).

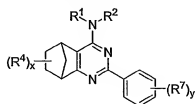
[0091] In preferred embodiments of any of formulae **II**, **II-A**, **II-B**, or **II-C**,  $z$  is 0-2. In other preferred embodiments of any of formulae **II**, **II-A**, **II-B**, or **II-C**,  $z$  is 0 and the ring is unsubstituted.

[0092] Preferred  $R^5$  groups of any of formulae **II**, **II-A**, **II-B**, or **II-C**, when present, are independently halogen, CN,  $\text{NO}_2$ , or an optionally substituted group selected from  $\text{C}_{1-6}$  alkyl, aryl,  $\text{aryl}(\text{C}_{1-6})\text{alkyl}$ ,  $-\text{N}(\text{R}')_2$ ,  $-\text{CH}_2\text{N}(\text{R}')_2$ ,  $\text{OR}'$ ,  $-\text{CH}_2\text{OR}'$ ,  $\text{SR}'$ ,  $-\text{CH}_2\text{SR}'$ ,  $\text{COOR}'$ ,  $-\text{NRCOR}'$ ,  $-(\text{CH}_2)_2\text{N}(\text{R}')_2$ ,  $-(\text{CH}_2)_2\text{OR}'$ ,  $-(\text{CH}_2)_2\text{SR}'$ ,  $-\text{COR}'$ ,  $-\text{CON}(\text{R}')_2$ , or  $-\text{S}(\text{O})_2\text{N}(\text{R}')_2$ . In more preferred embodiments of any of formulae **II**, **II-A**, **II-B**, or **II-C**,  $R^5$  groups are each

independently Cl, Br, F, CF<sub>3</sub>, Me, Et, CN, NO<sub>2</sub>, -COOH, NH<sub>2</sub>, -N(CH<sub>3</sub>)<sub>2</sub>, -N(Et)<sub>2</sub>, -N(iPr)<sub>2</sub>, -O(CH<sub>2</sub>)<sub>2</sub>OCH<sub>3</sub>, -CONH<sub>2</sub>, -COOCH<sub>3</sub>, -OH, -CH<sub>2</sub>OH, -NHCOCH<sub>3</sub>, -SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, piperidinyl, piperizinyl, morpholino, or an optionally substituted group selected from C<sub>1-4</sub> alkoxy, phenyl, phenyloxy, benzyl, or benzyloxy. Most preferred R<sup>5</sup> groups of any of formulae II, II-A, II-B, or II-C include those shown below in Table 2.

[0093] In preferred embodiments of any of formulae II, II-A, II-B, or II-C, R<sup>6</sup> groups are independently hydrogen, or an optionally substituted group selected from C<sub>1-6</sub> alkyl, aryl, aryl(C<sub>1-6</sub>) alkyl, -N(R')<sub>2</sub>, -CH<sub>2</sub>N(R')<sub>2</sub>, -CH<sub>2</sub>OR', -CH<sub>2</sub>SR', -(CH<sub>2</sub>)<sub>2</sub>N(R')<sub>2</sub>, -(CH<sub>2</sub>)<sub>2</sub>OR', -(CH<sub>2</sub>)<sub>2</sub>SR', -COR', -CON(R')<sub>2</sub>, or -S(O)<sub>2</sub>N(R')<sub>2</sub>. In more preferred embodiments of any of formulae II, II-A, II-B, or II-C, R<sup>6</sup> groups are each independently H, Me, CF<sub>3</sub>, ethyl, propyl, butyl, pentyl, CO(C<sub>1-4</sub> alkyl), -CONH<sub>2</sub>, -COO(C<sub>1-4</sub> alkyl), -CH<sub>2</sub>OH, -SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, or optionally substituted phenyl. Most preferred R<sup>6</sup> groups of any of formulae II, II-A, II-B, or II-C include those shown below in Table 2.

[0094] In preferred embodiments of any of formulae II, II-A, II-B, or II-C, x is 0, 1, or 2 and each R<sup>4</sup> is independently hydrogen, halogen, CN, NO<sub>2</sub>, or an optionally substituted group selected from C<sub>1-6</sub> alkyl, aryl, aryl(C<sub>1-6</sub>)alkyl, -N(R')<sub>2</sub>, -CH<sub>2</sub>N(R')<sub>2</sub>, OR', -CH<sub>2</sub>OR', SR', -CH<sub>2</sub>SR', COOR', -NRCOR', -(CH<sub>2</sub>)<sub>2</sub>N(R')<sub>2</sub>, -(CH<sub>2</sub>)<sub>2</sub>OR', -(CH<sub>2</sub>)<sub>2</sub>SR', -COR', -CON(R')<sub>2</sub>, or -S(O)<sub>2</sub>N(R')<sub>2</sub>. In more preferred embodiments of any of formulae II, II-A, II-B, or II-C, each R<sup>3</sup> is independently H, Cl, Br, F, CF<sub>3</sub>, Me, Et, CN, NO<sub>2</sub>, -COOH, NH<sub>2</sub>, -N(CH<sub>3</sub>)<sub>2</sub>, -N(Et)<sub>2</sub>, -N(iPr)<sub>2</sub>, -O(CH<sub>2</sub>)<sub>2</sub>OCH<sub>3</sub>, -CONH<sub>2</sub>, -COOCH<sub>3</sub>, -OH, -CH<sub>2</sub>OH, -NHCOCH<sub>3</sub>, -SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, piperidinyl, piperizinyl, morpholino, or an optionally substituted group selected from C<sub>1-4</sub> alkoxy, phenyl, phenyloxy, benzyl, or benzyloxy. In still other preferred embodiments of any of formulae II, II-A, II-B, or II-C, two occurrences of R<sup>4</sup>, taken together form an optionally substituted 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In some preferred embodiments of any of formulae II, II-A, II-B, or II-C, two occurrences of R<sup>4</sup>, taken together form a cycloalkyl group and compounds have the structure as shown in formula II-B-i:

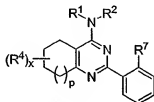


**II-B-i**

[0095] Other preferred  $R^4$  groups of any of formulae **II**, **II-A**, **II-B**, or **II-C** include those shown below in Table 2.

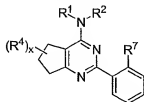
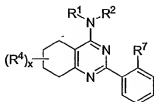
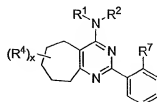
[0096] In preferred embodiments,  $y$  is 0-2. In other preferred embodiments,  $y$  is 0 and Ring A is unsubstituted. In preferred embodiments,  $R^7$  groups are independently hydrogen, halogen, CN,  $\text{NO}_2$ , or an optionally substituted group selected from  $\text{C}_{1-6}$  alkyl, aryl, aryl( $\text{C}_{1-6}$ )alkyl,  $-\text{N}(\text{R}')_2$ ,  $-\text{CH}_2\text{N}(\text{R}')_2$ ,  $\text{OR}'$ ,  $-\text{CH}_2\text{OR}'$ ,  $\text{SR}'$ ,  $-\text{CH}_2\text{SR}'$ ,  $\text{COOR}'$ ,  $-\text{NRCOR}'$ ,  $-(\text{CH}_2)_2\text{N}(\text{R}')_2$ ,  $-(\text{CH}_2)_2\text{OR}'$ ,  $-(\text{CH}_2)_2\text{SR}'$ ,  $-\text{COR}'$ ,  $-\text{CON}(\text{R}')_2$ , or  $-\text{S}(\text{O})_2\text{N}(\text{R}')_2$ . In more preferred embodiments,  $R^7$  groups are each independently H, Cl, Br, F,  $\text{CF}_3$ , Me, Et, CN,  $\text{NO}_2$ ,  $-\text{COOH}$ ,  $\text{NH}_2$ ,  $-\text{N}(\text{CH}_3)_2$ ,  $-\text{N}(\text{Et})_2$ ,  $-\text{N}(\text{iPr})_2$ ,  $-\text{O}(\text{CH}_2)_2\text{OCH}_3$ ,  $-\text{CONH}_2$ ,  $-\text{COOCH}_3$ ,  $-\text{OH}$ ,  $-\text{CH}_2\text{OH}$ ,  $-\text{NHCOCH}_3$ ,  $-\text{SO}_2\text{NH}_2$ ,  $\text{SO}_2\text{N}(\text{CH}_3)_2$ , piperidinyl, piperiziny, morpholino, or an optionally substituted group selected from  $\text{C}_{1-4}$  alkoxy, phenyl, phenyloxy, benzyl, or benzyloxy. Most preferred  $R^7$  groups include those shown below in Table 2.

[0097] In yet other preferred embodiments  $y$  is 1 and compounds have the general formula **III**:

**III**

wherein  $R^1$ ,  $R^2$ ,  $R^4$ ,  $x$ , and  $p$  are described generally above and herein, and  $R^7$  is halogen, CN,  $\text{NO}_2$ , or an optionally substituted group selected from  $\text{C}_{1-4}$  alkyl, aryl, aralkyl,  $-\text{N}(\text{R}')_2$ ,  $-\text{CH}_2\text{N}(\text{R}')_2$ ,  $-\text{OR}'$ ,  $-\text{CH}_2\text{OR}'$ ,  $-\text{SR}'$ ,  $-\text{CH}_2\text{SR}'$ ,  $-\text{COOR}'$ ,  $-\text{NRCOR}'$ ,  $-\text{CON}(\text{R}')_2$ , or  $-\text{S}(\text{O})_2\text{N}(\text{R}')_2$ .

[0098] In other preferred embodiments  $p$  is 0, 1, or 2, and compounds have the structure of formula **III-A**, **III-B**, or **III-C**:

**III-A****III-B****III-C**

wherein  $R^1$ ,  $R^2$ ,  $R^4$ , and  $x$  are described generally above and herein, and each  $R^7$  is independently halogen, CN,  $NO_2$ , or an optionally substituted group selected from  $C_{1-4}$  alkyl, aryl, aralkyl,  $-N(R')_2$ ,  $-CH_2N(R')_2$ ,  $-OR'$ ,  $-CH_2OR'$ ,  $-SR'$ ,  $-CH_2SR'$ ,  $-COOR'$ ,  $-NRCOR'$ ,  $-CON(R')_2$ , or  $-S(O)_2N(R')_2$ .

**[0099]** In one embodiment of formula III-A,  $x$  is 0,  $R^7$  is hydroxy,  $R^1$  and  $R^2$  are both  $C_{1-4}$  alkyl, or  $R^1$  and  $R^2$ , taken together, form a pyrrolidyl, piperidinyl, or morpholinyl ring. In another embodiment of formula IIIA,  $x$  is 0,  $R^7$  is hydroxy,  $R^1$  and  $R^2$  are both methyl, or  $R^1$  and  $R^2$ , taken together, form a pyrrolidyl or piperidinyl ring. Or, in another embodiment,  $x$  is 0,  $R^7$  is hydroxy,  $R^1$  and  $R^2$  are both methyl, or  $R^1$  and  $R^2$ , taken together, form a pyrrolidyl ring.

**[00100]** In one embodiment of formula III-B,

**[00101]** In still other preferred embodiments compounds of the invention are defined according to formula III, III-A, III-B, or III-C and one or more of, or all of,  $R^1$ ,  $R^2$ ,  $R^4$  or  $x$  are further defined according to one or more of, or all of, the following groups:

- a.  $R^1$  and  $R^2$  are each independently selected from a 5- or 6-membered aryl ring having 0-5 heteroatoms independently selected from N, O, or S, a 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from N, O, or S, or an optionally substituted  $C_{1-4}$  aliphatic group, wherein one or more methylene units in the  $C_{1-4}$  aliphatic group are optionally and independently replaced with NR, O, (CO)O, O(CO), NR(CO), (CO)NR,  $SO_2(NR)$ , or  $(NR)SO_2$ ; and
- b.  $x$  is 0, 1, or 2, and  $R^4$  is hydrogen, halogen, CN,  $NO_2$ , or an optionally substituted group selected from  $C_{1-6}$  alkyl, aryl, aryl( $C_{1-6}$ )alkyl,  $-N(R')_2$ ,  $-CH_2N(R')_2$ ,  $OR'$ ,  $-CH_2OR'$ ,  $SR'$ ,  $-CH_2SR'$ ,  $COOR'$ ,  $-NRCOR'$ ,  $-(CH_2)_2N(R')_2$ ,  $-(CH_2)_2OR'$ ,  $-(CH_2)_2SR'$ ,  $-COR'$ ,  $-CON(R')_2$ , or  $-S(O)_2N(R')_2$ .

**[00102]** In still other preferred embodiments compounds of the invention are defined according to formula III, III-A, III-B, or III-C and one or more of, or all of,  $R^1$ ,  $R^2$ ,  $R^4$ ,  $x$ , or  $R^7$  are further defined according to one or more of, or all of, the following groups:

- a.  $R^1$  and  $R^2$  are each independently optionally substituted methyl, ethyl, cyclopropyl, n-propyl, propenyl, cyclobutyl, (CO)OCH<sub>2</sub>CH<sub>3</sub>, (CH<sub>2</sub>)<sub>2</sub>OCH<sub>3</sub>, CH<sub>2</sub>(CO)OCH<sub>2</sub>CH<sub>3</sub>, CH<sub>2</sub>(CO)OCH<sub>3</sub>, CH(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>3</sub>, or t-butyl, or n-butyl; and

- b.  $x$  is 0, 1, or 2, and each  $R^4$  is independently H, Cl, Br, F,  $CF_3$ , Me, Et, CN,  $NO_2$ ,  $-COOH$ ,  $NH_2$ ,  $-N(CH_3)_2$ ,  $-N(Et)_2$ ,  $-N(iPr)_2$ ,  $-O(CH_2)_2OCH_3$ ,  $-CONH_2$ ,  $-COOCH_3$ ,  $-OH$ ,  $-CH_2OH$ ,  $-NHCOCH_3$ ,  $-SO_2NH_2$ ,  $SO_2N(CH_3)_2$ , piperidinyl, piperizinyl, morpholino, or an optionally substituted group selected from  $C_{1-4}$  alkoxy, phenyl, phenyloxy, benzyl, or benzyloxy.

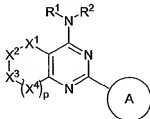
[00103] In still other preferred embodiments compounds of the invention are defined according to formula III, III-A, III-B, or III-C and one or more of, or all of,  $R^1$ ,  $R^2$ ,  $R^4$ ,  $x$ , or  $R^7$  are further defined according to one or more of, or all of, the following groups:

- $R^1$  and  $R^2$  are each independently optionally substituted methyl, ethyl, cyclopropyl, n-propyl, propenyl, cyclobutyl,  $(CO)OCH_2CH_3$ ,  $(CH_2)_2OCH_3$ ,  $CH_2(CO)OCH_2CH_3$ ,  $CH_2(CO)OCH_3$ ,  $CH(CH_3)CH_2CH_3$ , or t-butyl, or n-butyl;
- $x$  is 0, 1, or 2, and each  $R^4$  is independently H, Cl, Br, F,  $CF_3$ , Me, Et, CN,  $NO_2$ ,  $-COOH$ ,  $NH_2$ ,  $-N(CH_3)_2$ ,  $-N(Et)_2$ ,  $-N(iPr)_2$ ,  $-O(CH_2)_2OCH_3$ ,  $-CONH_2$ ,  $-COOCH_3$ ,  $-OH$ ,  $-CH_2OH$ ,  $-NHCOCH_3$ ,  $-SO_2NH_2$ ,  $SO_2N(CH_3)_2$ , piperidinyl, piperizinyl, morpholino, or an optionally substituted group selected from  $C_{1-4}$  alkoxy, phenyl, phenyloxy, benzyl, or benzyloxy; and
- $R^7$  is Cl, Br, F,  $CF_3$ , Me, Et, CN,  $NO_2$ ,  $-COOH$ ,  $NH_2$ ,  $-N(CH_3)_2$ ,  $-N(Et)_2$ ,  $-N(iPr)_2$ ,  $-O(CH_2)_2OCH_3$ ,  $-CONH_2$ ,  $-COOCH_3$ ,  $-OH$ ,  $-CH_2OH$ ,  $-NHCOCH_3$ ,  $-SO_2NH_2$ ,  $SO_2N(CH_3)_2$ , piperidinyl, piperizinyl, morpholino, or an optionally substituted group selected from  $C_{1-4}$  alkoxy, phenyl, phenyloxy, benzyl, or benzyloxy.

[00104] In one embodiment, formula III-C has one or more of the following features:

- $R^7$  is hydroxy;
- $R^1$  and  $R^2$  are both  $C_{1-4}$  alkyl, preferably, methyl, or  $R^1$  and  $R^2$ , taken together, form a pyrrolinyl ring or morpholinyl ring; and
- $x$  is 0.

[00105] In certain embodiments, the present invention provides a compound of formula IV:



## IV

or a pharmaceutically acceptable salt thereof, wherein:

p is 0, 1 or 2;

X<sup>1</sup>, X<sup>2</sup>, X<sup>3</sup> and X<sup>4</sup> are each independently selected from NR<sup>3</sup>, C=O, CHR<sup>4</sup>, S, O, S=O, or SO<sub>2</sub>, as valency and stability permit, provided that that X<sup>1</sup>, X<sup>2</sup>, X<sup>3</sup> and X<sup>4</sup> are not each simultaneously CHR<sup>4</sup>;

R<sup>1</sup> and R<sup>2</sup> are each independently hydrogen, or an optionally substituted group selected from C<sub>1-6</sub> aliphatic, a 5-6 membered aryl ring having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or R<sup>1</sup> and R<sup>2</sup>, taken together with the nitrogen atom to which they are bound, form an optionally substituted 3-8 membered heterocyclyl or heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein R<sup>1</sup>, R<sup>2</sup>, or any ring formed by R<sup>1</sup> and R<sup>2</sup> taken together, are each independently optionally substituted at one or more carbon atoms with 0-4 occurrences of -R<sup>5</sup>, and at one or more substitutable nitrogen atoms with -R<sup>6</sup>;

Ring A is a 5-6 membered monocyclic or 8-10 membered bicyclic aryl ring having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, optionally substituted at one or more carbon atoms with 0-5 occurrences of -R<sup>7</sup>, and at one or more substitutable nitrogen atoms with -R<sup>8</sup>;

each occurrence of R<sup>4</sup>, R<sup>5</sup>, and R<sup>7</sup> is independently Q-R<sup>X</sup>; wherein Q is a bond or is a C<sub>1-6</sub> alkylidene chain wherein up to two non-adjacent methylene units of Q are optionally and independently replaced by CO, CO<sub>2</sub>, COCO, CONR, OCONR, NRNR, NRNRCO, NRCO, NRCO<sub>2</sub>, NRCONR, SO, SO<sub>2</sub>, NRSO<sub>2</sub>, SO<sub>2</sub>NR, NRSO<sub>2</sub>NR, O, S, or NR;

each occurrence of R<sup>X</sup> is independently selected from R', halogen, NO<sub>2</sub>, or CN;

each occurrence of R is independently selected from hydrogen or an optionally substituted C<sub>1-6</sub> aliphatic group;

each occurrence of R' is independently selected from hydrogen or an optionally substituted group selected from C<sub>1-8</sub> aliphatic, C<sub>6-10</sub> aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclyl ring having 3-10 ring atoms, or wherein R and R' taken together with the atom(s) to which they are bound, or two occurrences of R' taken together with the atom(s) to



which they are bound, form a 5-8 membered cycloalkyl, heterocyclyl, aryl, or heteroaryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and

each occurrence of  $R^3$ ,  $R^6$  or  $R^8$  is independently  $R^1$ ,  $-\text{COR}'$ ,  $-\text{CO}_2(\text{C}_{1-6} \text{ aliphatic})$ ,  $-\text{CON}(\text{R}')_2$ , or  $-\text{SO}_2\text{R}'$ .

**[00106]** In certain embodiments, for compounds of formula IV:

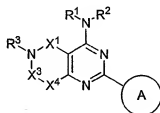
- a)  $R^1$  is not hydrogen when  $R^2$  is optionally substituted indazol-3-yl;
- b)  $R^1$  is not hydrogen when  $R^2$  is optionally substituted pyrazol-3-yl;
- c)  $R^1$  is not hydrogen when  $R^2$  is 1,2,4-triazol-3-yl;
- d) when p is 1, then:
  - i) when  $R^1$  and  $R^2$ , taken together with the nitrogen atom, is N-morpholino, and Ring A is unsubstituted phenyl, then  $X^1$ ,  $X^2$ ,  $X^3$  and  $X^4$  are not, respectively:
    - 1)  $\text{CH}_2$ ,  $\text{CH}(\text{CH}_2)\text{Ph}$ ,  $\text{NR}^3$ , and  $\text{CHCH}_3$ ;
    - 2)  $\text{CH}_2$ ,  $\text{CH}_2$ ,  $\text{CH}_2$ , and S;
    - 3)  $\text{CH}_2$ , S,  $\text{CH}_2$ , and S;
    - 4)  $\text{CH}_2$ ,  $\text{CH}_2$ , S, and  $\text{CH}_2$ ;
    - 5)  $\text{CH}_2$ ,  $\text{CHMe}$ , S, and  $\text{CH}_2$ ; or
    - 6)  $\text{CHMe}$ ,  $\text{CH}_2$ ,  $\text{N}(\text{CH}_2)\text{Ph}$ , and  $\text{CH}_2$ ;
  - ii)  $R^1$  is not hydrogen, and  $R^2$  is not  $\text{CH}_2\text{Ph}$ ,  $(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{OH}$ , or  $-\text{CH}_2(1,3\text{-benzodioxol-5-yl})$  when Ring A is imidazol-1-yl;
  - iii) when  $R^1$  and  $R^2$ , taken together with the nitrogen atom, is N-piperidinyl then:
    - 1) when  $X^1$ ,  $X^2$  and  $X^3$  are  $\text{CH}_2$ , and  $X^4$  is S, then Ring A is not unsubstituted phenyl; and
    - 2) when  $X^1$ ,  $X^2$  and  $X^4$  are  $\text{CH}_2$ ; and  $X^3$  is S, then Ring A is not unsubstituted phenyl;
  - iv) when  $R^1$  and  $R^2$ , taken together with the nitrogen atom, is N-piperizinyl,  $X^1$ ,  $X^2$  and  $X^3$  are  $\text{CH}_2$ ; and  $X^4$  is S, then Ring A is not 3- $\text{NO}_2\text{Ph}$ , 4-pyridinyl, or unsubstituted phenyl;
  - v) when one of  $X^1$ ,  $X^2$ ,  $X^3$  or  $X^4$  is  $\text{NR}^3$  and the others of  $X^1$ ,  $X^2$ ,  $X^3$  or  $X^4$  are each  $\text{CH}_2$ , and  $R^1$  and  $R^2$  are each Me, H,  $\text{CH}_2\text{Ph}$ , or  $(\text{CH}_2)_2\text{NMe}_2$ , then Ring A is not pyrid-2-yl substituted at the 6-position;

- vi) when  $X^1$ ,  $X^2$ , and  $X^3$  are each  $\text{CH}_2$ ,  $X^4$  is S,  $R^1$  is H, and  $R^2$  is  $-\text{CH}_2\text{C}\equiv\text{CH}$ , then Ring A is not unsubstituted phenyl;
  - vii) when  $X^1$  is NMe;  $X^2$ ,  $X^3$  and  $X^4$  are each  $\text{CH}^2$ ,  $R^1$  is H, and  $R^2$  is unsubstituted phenyl, then Ring A is not unsubstituted phenyl; and
  - viii) when  $X^1$ ,  $X^2$  and  $X^4$  are each  $\text{CH}_2$ ;  $X^3$  is S,  $R^1$  and  $R^2$  are each Me, then Ring A is not unsubstituted phenyl; and
- e) when p is 0, then:
- i) when  $X^1$  is  $\text{CH}_2$ ,  $X^2$  is  $\text{NR}^3$ ,  $X^3$  is  $\text{C=O}$ ; or  $X^1$  is  $\text{C=O}$ ,  $X^2$  is  $\text{CHR}^4$ , and  $X^3$  is  $\text{NR}^3$ ; or  $X^2$  is  $\text{NR}^3$ ,  $X^2$  is  $\text{C=O}$ , and  $X^3$  is  $\text{CHR}^4$ ; or  $X^1$  is  $\text{CH}_2$ ,  $X^2$  is O, and  $X^3$  is  $\text{C=O}$ , then when  $R^1$  is hydrogen and  $R^2$  is unsubstituted phenyl or  $-\text{CH}_2\text{CH}_2\text{Cl}$ , or when  $R^1$  and  $R^2$ , taken together form optionally substituted piperazinyl, morpholino, piperidinyl, or pyrrolidinyl, then Ring A is not optionally substituted piperidinyl, piperazinyl, morpholino, or pyrrolidinyl;
  - ii) when  $X^1$  is  $\text{CHR}^4$ ,  $X^2$  is  $\text{SO}_2$ , and  $X^3$  is  $\text{CHR}^4$ , and  $R^1$  and  $R^2$ , taken together are piperazinyl, then Ring A is not unsubstituted phenyl;
  - iii) when  $X^1$  and  $X^2$  are  $\text{CHR}^4$ ,  $X^3$  is O,  $R^1$  is hydrogen, and  $R^2$  is  $-\text{C(=O)CH}_3$ , then Ring A is not substituted furyl;
  - iv) when  $X^1$  is S,  $X^2$  is  $\text{CHR}^4$ ,  $X^3$  is  $\text{CHR}^4$ ; or  $X^1$  is  $\text{CHR}^4$ ,  $X^2$  is S, and  $X^3$  is  $\text{CHR}^4$ ; or  $X^1$  and  $X^2$  are  $\text{CHR}^4$  and  $X^3$  is S, then Ring A is not optionally substituted N-linked morpholino, pyrrolidinyl, piperazinyl, piperidinyl, or is not unsubstituted phenyl or cyclopropyl;
  - v) when  $X^1$  is  $\text{CHR}^4$ ,  $X^2$  is  $\text{NR}^3$ ,  $X^3$  is  $\text{CHR}^4$ , and  $R^1$  and  $R^2$  are both methyl, then Ring A is not 6-methyl-2-pyridyl;
  - vi) when  $X^1$  is  $\text{NR}^3$ ,  $X^2$  is  $\text{C=O}$ ,  $X^2$  is  $\text{NR}^3$ , and  $R^1$  and  $R^2$  are both methyl, then Ring A is not unsubstituted phenyl; and
  - vii) when  $X^1$  and  $X^2$  are  $\text{CHR}^4$ ,  $X^3$  is  $\text{NR}^3$ ,  $R^1$  is hydrogen, and  $R^2$  is unsubstituted phenyl, then Ring A is not unsubstituted phenyl.

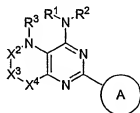
[00107] As described generally above, for compounds of formula IV, p is 0, 1, or 2, and  $X^1$ ,  $X^2$ ,  $X^3$  and  $X^4$  are each independently selected from  $\text{NR}^3$ ,  $\text{CHR}^4$ , S, O,  $\text{S=O}$ , or  $\text{SO}_2$ , as valency and stability permit, provided that when p is 1,  $X^1$ ,  $X^2$ ,  $X^3$  and  $X^4$  are not each simultaneously  $\text{CHR}^4$ , or when p is 0,  $X^1$ ,  $X^2$ , and  $X^3$  are not each simultaneously  $\text{CHR}^4$ .

[00108] In certain embodiments, p is 0 or 1.

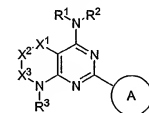
[00109] In certain preferred embodiments of formula IV, one or two of  $X^1$ ,  $X^2$ ,  $X^3$ , or  $X^4$  is  $NR^3$ , S, O,  $S=O$ , or  $SO_2$ , and the remaining one, two, or three are each  $CHR^4$ . In more preferred embodiments of formula IV, one of  $X^1$ ,  $X^2$ ,  $X^3$ , or  $X^4$  is  $NR^3$ , S, or O, and the remaining two (when p is 0) or three (when p is 1) are each  $CHR^4$ , and compounds have one of the following structures:



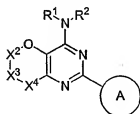
IV-A



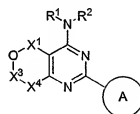
IV-B



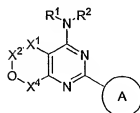
IV-C



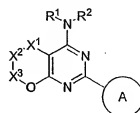
IV-D



IV-E

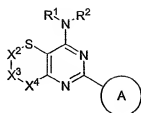


IV-F

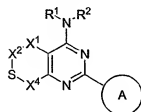


IV-G

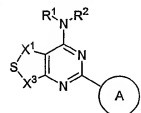
IV-H



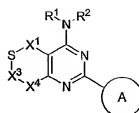
IV-I



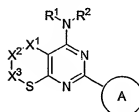
IV-K



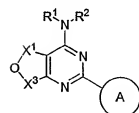
IV-M



IV-J



IV-L



IV-N

wherein each  $R^1$ ,  $R^2$ , Ring A,  $X^1$ ,  $X^2$ ,  $X^3$  and  $X^4$  is as defined above and herein.

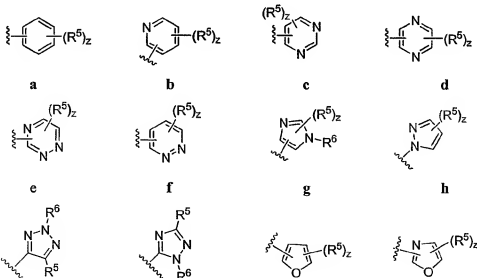
**[00110]** In one embodiment of formula IV-I, formula IV-J, formula IV-K, formula IV-L, or formula IV-M, the sulfur ring atom is replaced with sulfoxo. Or, the sulfur ring atom is replaced with sulfonyl.

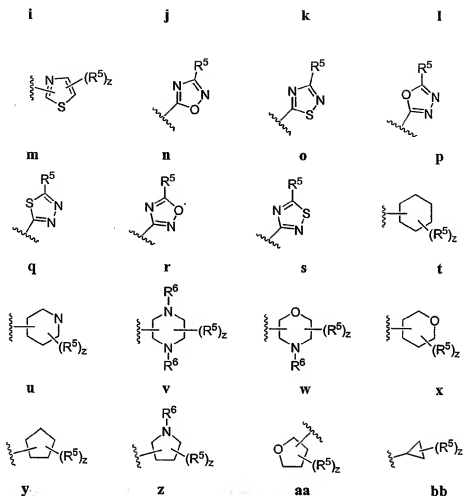
**[00111]** In certain preferred embodiments of formula IV, neither  $R^1$  nor  $R^2$  is hydrogen, and  $R^1$  and  $R^2$  are each independently selected from a 5- or 6-membered aryl ring having 0-5 heteroatoms independently selected from N, O, or S, a 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from N, O, or S, or an optionally substituted  $C_{1-4}$  aliphatic group, wherein one or more methylene units in the  $C_{1-4}$  aliphatic group are optionally and independently replaced with NR, O, (CO)O, O(CO), NR(CO), (CO)NR,  $SO_2$ (NR), or (NR) $SO_2$ . In more preferred embodiments of formula IV, both  $R^1$  and  $R^2$  are an optionally substituted  $C_{1-4}$  aliphatic group, wherein one or more methylene units in the  $C_{1-4}$  aliphatic group are optionally and independently replaced with NR, O, (CO)O, O(CO), NR(CO),

(CO)NR, SO<sub>2</sub>(NR), or (NR)SO<sub>2</sub>. In yet other preferred embodiments of formula IV, when R<sup>1</sup> and R<sup>2</sup> are an optionally substituted C<sub>1-4</sub> aliphatic group, wherein one or more methylene units in the C<sub>1-4</sub> aliphatic group are optionally and independently replaced with NR, O, (CO)O, O(CO), NR(CO), (CO)NR, SO<sub>2</sub>(NR), or (NR)SO<sub>2</sub>, preferred R<sup>1</sup> and R<sup>2</sup> groups are optionally substituted methyl, ethyl, cyclopropyl, n-propyl, propenyl, cyclobutyl, (CO)OCH<sub>2</sub>CH<sub>3</sub>, (CH<sub>2</sub>)<sub>2</sub>OCH<sub>3</sub>, CH<sub>2</sub>(CO)OCH<sub>2</sub>CH<sub>3</sub>, CH<sub>2</sub>(CO)OCH<sub>3</sub>, CH(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>3</sub>, or t-butyl, or n-butyl. Most preferred R<sup>1</sup> and R<sup>2</sup> groups of formula IV include those shown below in Table 2:

[00112] In other preferred embodiments of formula IV, one of R<sup>1</sup> or R<sup>2</sup> is hydrogen and the other of R<sup>1</sup> or R<sup>2</sup> is a 5-6 membered aryl ring having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In other embodiments of formula IV, one of R<sup>1</sup> or R<sup>2</sup> is hydrogen, and the other of R<sup>1</sup> or R<sup>2</sup> is an optionally substituted C<sub>1-4</sub> aliphatic group, wherein one or more methylene units in the C<sub>1-4</sub> aliphatic group are optionally and independently replaced with NR, O, (CO)O, O(CO), NR(CO), (CO)NR, SO<sub>2</sub>(NR), or (NR)SO<sub>2</sub>.

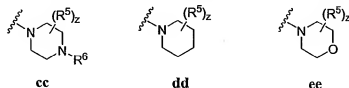
[00113] For those embodiments described above and herein for compounds of formula IV where R<sup>1</sup> or R<sup>2</sup> is a 5- or 6-membered aryl ring having 0-5 heteroatoms independently selected from N, O, or S, or a 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from N, O, or S, preferred R<sup>1</sup> and R<sup>2</sup> groups are selected from:





wherein each  $R^5$  and  $R^6$  is as previously defined and each  $z$  is independently 0-4. Most preferred rings include those shown below in Table 2.

**[00114]** In still other embodiments for compounds of formula IV,  $R^1$  and  $R^2$ , taken together with the nitrogen atom to which they are bound, form an optionally substituted 3-8 membered heterocyclyl ring having 1-3 heteroatoms independently selected from nitrogen or oxygen. In certain preferred embodiments,  $R^1$  and  $R^2$  are taken together with the nitrogen atom to which they are bound and form a 3-8 membered heterocyclyl group selected from:





ff



gg



hh

wherein each  $R^5$  and  $R^6$  is as previously defined and each  $z$  is independently 0-4.

[00115] In other preferred embodiments of formula IV,  $R^1$  and  $R^2$  taken together are optionally substituted pyrrolidin-1-yl (ff), piperidin-1-yl (dd), piperazin-1-yl (cc), or morpholin-4-yl (ee).

[00116] In preferred embodiments of formula IV,  $z$  is 0-2. In other preferred embodiments of formula IV,  $z$  is 0 and the ring is unsubstituted.

[00117] Preferred  $R^5$  groups of formula IV, when present, are independently halogen, CN,  $\text{NO}_2$ , or an optionally substituted group selected from  $\text{C}_{1-6}$  alkyl, aryl,  $\text{aryl}(\text{C}_{1-6})\text{alkyl}$ ,  $-\text{N}(\text{R}')_2$ ,  $-\text{CH}_2\text{N}(\text{R}')_2$ ,  $\text{OR}'$ ,  $-\text{CH}_2\text{OR}'$ ,  $\text{SR}'$ ,  $-\text{CH}_2\text{SR}'$ ,  $\text{COOR}'$ ,  $-\text{NRCOR}'$ ,  $-(\text{CH}_2)_2\text{N}(\text{R}')_2$ ,  $-(\text{CH}_2)_2\text{OR}'$ ,  $-(\text{CH}_2)_2\text{SR}'$ ,  $-\text{COR}'$ ,  $-\text{CON}(\text{R}')_2$ ,  $\text{SO}_2\text{R}'$ , or  $-\text{SO}_2\text{N}(\text{R}')_2$ . In more preferred embodiments of formula IV,  $R^5$  groups are each independently Cl, Br, F,  $\text{CF}_3$ , Me, Et, CN,  $\text{NO}_2$ ,  $-\text{COOH}$ ,  $\text{NH}_2$ ,  $-\text{N}(\text{CH}_3)_2$ ,  $-\text{N}(\text{Et})_2$ ,  $-\text{N}(\text{iPr})_2$ ,  $-\text{O}(\text{CH}_2)_2\text{OCH}_3$ ,  $-\text{CO}(\text{C}_{1-4}\text{ alkyl})$ ,  $-\text{CONH}_2$ ,  $-\text{COOCH}_3$ ,  $-\text{OH}$ ,  $-\text{CH}_2\text{OH}$ ,  $-\text{NHCOCCH}_3$ ,  $-\text{SO}_2(\text{C}_{1-4}\text{ alkyl})$ ,  $-\text{SO}_2\text{NH}_2$ ,  $-\text{SO}_2\text{N}(\text{CH}_3)_2$ , piperidinyl, piperizinyl, morpholino, or an optionally substituted group selected from  $\text{C}_{1-4}$  alkoxy, phenyl, phenyloxy, benzyl, or benzyloxy. Most preferred  $R^5$  groups of formula IV include those shown below in Table 2.

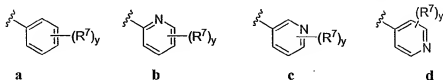
[00118] In preferred embodiments of formula IV,  $R^6$  groups are independently hydrogen, or an optionally substituted group selected from  $\text{C}_{1-6}$  alkyl, aryl,  $\text{aryl}(\text{C}_{1-6})\text{alkyl}$ ,  $-\text{N}(\text{R}')_2$ ,  $-\text{CH}_2\text{N}(\text{R}')_2$ ,  $-\text{CH}_2\text{OR}'$ ,  $-\text{CH}_2\text{SR}'$ ,  $-(\text{CH}_2)_2\text{N}(\text{R}')_2$ ,  $-(\text{CH}_2)_2\text{OR}'$ ,  $-(\text{CH}_2)_2\text{SR}'$ ,  $-\text{COR}'$ ,  $-\text{CON}(\text{R}')_2$ ,  $\text{SO}_2\text{R}'$ , or  $-\text{S}(\text{O})_2\text{N}(\text{R}')_2$ . In more preferred embodiments of formula IV,  $R^6$  groups are each independently H, Me,  $\text{CF}_3$ , ethyl, propyl, butyl, pentyl,  $\text{CO}(\text{C}_{1-4}\text{ alkyl})$ ,  $-\text{CONH}_2$ ,  $-\text{COO}(\text{C}_{1-4}\text{ alkyl})$ ,  $-\text{CH}_2\text{OH}$ ,  $-\text{SO}_2(\text{C}_{1-4}\text{ alkyl})$ ,  $-\text{SO}_2\text{NH}_2$ ,  $\text{SO}_2\text{N}(\text{CH}_3)_2$ , or optionally substituted phenyl or benzyl. Most preferred  $R^6$  groups of formula IV include those shown below in Table 2.

[00119] In preferred embodiments of formula IV,  $R^4$  groups are independently hydrogen, halogen, CN,  $\text{NO}_2$ , or an optionally substituted group selected from  $\text{C}_{1-6}$  alkyl, aryl,  $\text{aryl}(\text{C}_{1-6})\text{alkyl}$ ,  $-\text{N}(\text{R}')_2$ ,  $-\text{CH}_2\text{N}(\text{R}')_2$ ,  $\text{OR}'$ ,  $-\text{CH}_2\text{OR}'$ ,  $\text{SR}'$ ,  $-\text{CH}_2\text{SR}'$ ,  $\text{COOR}'$ ,  $-\text{NRCOR}'$ ,  $-(\text{CH}_2)_2\text{N}(\text{R}')_2$ ,  $-(\text{CH}_2)_2\text{OR}'$ ,  $-(\text{CH}_2)_2\text{SR}'$ ,  $-\text{COR}'$ ,  $-\text{CON}(\text{R}')_2$ ,  $\text{SO}_2\text{R}'$ , or  $-\text{SO}_2\text{N}(\text{R}')_2$ . In more preferred

embodiments of formula IV,  $R^4$  groups are each independently H, Cl, Br, F,  $CF_3$ , Me, Et, CN,  $NO_2$ ,  $-COOH$ ,  $NH_2$ ,  $-N(CH_3)_2$ ,  $-N(Et)_2$ ,  $-N(iPr)_2$ ,  $-O(CH_2)_2OCH_3$ ,  $-CO(C_1-C_4alkyl)$ ,  $-CONH_2$ ,  $-COOCH_3$ ,  $-OH$ ,  $-CH_2OH$ ,  $-NHCOCH_3$ ,  $-SO_2(C_1-C_4alkyl)$ ,  $-SO_2NH_2$ ,  $-SO_2N(CH_3)_2$ , piperidinyl, piperizinyl, morpholino, or an optionally substituted group selected from  $C_{1-4}$  alkoxy, phenyl, phenyloxy, benzyl, or benzyloxy. Most preferred  $R^4$  groups of formula IV include those shown below in Table 2.

**[00120]** In preferred embodiments of formula IV,  $R^3$  groups are independently hydrogen, or an optionally substituted group selected from  $C_{1-6}$  alkyl, aryl,  $aryl(C_{1-6}alkyl)$ ,  $-N(R')_2$ ,  $-CH_2N(R')_2$ ,  $-CH_2OR'$ ,  $-CH_2SR'$ ,  $-(CH_2)_2N(R')_2$ ,  $-(CH_2)_2OR'$ ,  $-(CH_2)_2SR'$ ,  $-COR'$ ,  $-CON(R')_2$ ,  $SO_2R'$ , or  $-S(O)_2N(R')_2$ . In more preferred embodiments of formula IV,  $R^3$  groups are each independently H, Me,  $CF_3$ , ethyl, propyl, butyl, pentyl,  $CO(C_1-C_4alkyl)$ ,  $-CONH_2$ ,  $-COO(C_1-C_4alkyl)$ ,  $-CH_2OH$ ,  $-SO_2(C_1-C_4alkyl)$ ,  $-SO_2NH_2$ ,  $SO_2N(CH_3)_2$ , or optionally substituted phenyl or benzyl. Most preferred  $R^3$  groups of formula IV include those shown below in Table 2.

**[00121]** As described generally above of formula IV, Ring A is a 5-6 membered aryl ring having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, optionally substituted at one or more carbon atoms with 0-5 occurrences of  $-R^7$ , and at one or more substitutable nitrogen atoms with  $-R^8$ . In certain embodiments, for compounds of formula IV or compounds of formulae IV-A through IV-N, Ring A is a phenyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, pyrrolyl, piperidinyl, indolyl, indazolyl, benzotriazolyl, pyrazolyl, benzopyrazolyl, imidazolyl, benzimidazolyl, thiazolyl, benzthiazolyl, oxazolyl, benzoxazolyl, isoxazolyl, benzisoxazolyl, isothiazolyl, benzisothiazolyl, triazolyl, benzotriazolyl, thiadiazolyl, thienyl, benzothienyl, furanoyl, benzofuranoyl, or triazinyl ring, each optionally substituted at one or more carbon atoms with 0-5 occurrences of  $-R^7$ , and at one or more substitutable nitrogen atoms with  $-R^8$ . It will be appreciated that Ring A can be attached to the pyrimidinyl ring through any available carbon or nitrogen atom (e.g., a thiazole ring can be attached in the 2-, 4-, or 5-position). In certain preferred embodiments of formula IV, Ring A is optionally substituted phenyl, 2-pyridyl, 3-pyridyl, or 4-pyridyl:





wherein each y is independently 0-5 and each R<sup>7</sup> is as defined generally above.

**[00122]** In preferred embodiments of formula IV, y is 0-2. In other preferred embodiments of formula IV, y is 0 and Ring A is unsubstituted.

**[00123]** In preferred embodiments of formula IV, R<sup>7</sup> groups are independently hydrogen, halogen, CN, NO<sub>2</sub>, or an optionally substituted group selected from C<sub>1-6</sub> alkyl, aryl, aryl(C<sub>1-6</sub>)alkyl, -N(R')<sub>2</sub>, -CH<sub>2</sub>N(R')<sub>2</sub>, OR', -CH<sub>2</sub>OR', SR', -CH<sub>2</sub>SR', COOR', -NRCOR', -(CH<sub>2</sub>)<sub>2</sub>N(R')<sub>2</sub>, -(CH<sub>2</sub>)<sub>2</sub>OR', -(CH<sub>2</sub>)<sub>2</sub>SR', -COR', -CON(R')<sub>2</sub>, SO<sub>2</sub>R', or -SO<sub>2</sub>N(R')<sub>2</sub>. In more preferred embodiments of formula IV, R<sup>7</sup> groups are each independently H, Cl, Br, F, CF<sub>3</sub>, Me, Et, CN, NO<sub>2</sub>, -COOH, NH<sub>2</sub>, -N(CH<sub>3</sub>)<sub>2</sub>, -N(Et)<sub>2</sub>, -N(iPr)<sub>2</sub>, -O(CH<sub>2</sub>)<sub>2</sub>OCH<sub>3</sub>, -CO(C<sub>1-4</sub>alkyl), -CONH<sub>2</sub>, -COOCH<sub>3</sub>, -OH, -CH<sub>2</sub>OH, -NHCOCH<sub>3</sub>, -SO<sub>2</sub>(C<sub>1-4</sub>alkyl), -SO<sub>2</sub>NH<sub>2</sub>, -SO<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, piperidinyl, piperiziny, morpholino, or an optionally substituted group selected from C<sub>1-4</sub> alkoxy, phenyl, phenyloxy, benzyl, or benzyloxy. Most preferred R<sup>7</sup> groups of formula IV include those shown below in Table 2.

**[00124]** In preferred embodiments of formula IV, R<sup>8</sup> groups are independently hydrogen, or an optionally substituted group selected from C<sub>1-6</sub> alkyl, aryl, aryl(C<sub>1-6</sub>)alkyl, -N(R')<sub>2</sub>, -CH<sub>2</sub>N(R')<sub>2</sub>, -CH<sub>2</sub>OR', -CH<sub>2</sub>SR', -(CH<sub>2</sub>)<sub>2</sub>N(R')<sub>2</sub>, -(CH<sub>2</sub>)<sub>2</sub>OR', -(CH<sub>2</sub>)<sub>2</sub>SR', -COR', -CON(R')<sub>2</sub>, SO<sub>2</sub>R', or -S(O)<sub>2</sub>N(R')<sub>2</sub>. In more preferred embodiments of formula IV, R<sup>8</sup> groups are each independently H, Me, CF<sub>3</sub>, ethyl, propyl, butyl, pentyl, CO(C<sub>1-4</sub>alkyl), -CONH<sub>2</sub>, -COO(C<sub>1-4</sub>alkyl), -CH<sub>2</sub>OH, -SO<sub>2</sub>(C<sub>1-4</sub>alkyl), -SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, or optionally substituted phenyl or benzyl. Most preferred R<sup>8</sup> groups of formula IV include those shown below in Table 2.

**[00125]** In one embodiment of formula IV-A, R<sup>1</sup> hydrogen or methyl, and R<sup>2</sup> is methyl, 5-methyl-pyrazol-3-yl, 5-fluoro-benzopyrazol-3-yl, or benzopyrazol-3-yl, X<sup>1</sup>, X<sup>3</sup>, and X<sup>4</sup> each is CH<sub>2</sub>, R<sup>3</sup> is hydrogen, acyl, 1-oxo-2-methoxy-ethyl, 1-oxo-propyl, methylsulfonyl, ethylsulfonyl, benzyl, and ring A is phenyl optionally substituted with halo, trifluoromethyl, hydroxy, C<sub>1-4</sub> alkyl, or C<sub>1-4</sub> alkoxy, preferably, methoxy, or ring A is 2,3-Dihydro-benzo[1,4]dioxin-3-yl.

**[00126]** In one embodiment of formula IV-A, R<sup>1</sup> hydrogen or methyl, and R<sup>2</sup> is methyl, 5-methyl-pyrazol-3-yl, 5-fluoro-benzopyrazol-3-yl, or benzopyrazol-3-yl, X<sup>1</sup>, X<sup>3</sup>, and X<sup>4</sup> each is CH<sub>2</sub>, R<sup>3</sup> is hydrogen or benzyl, and ring A is phenyl optionally substituted with halo, trifluoromethyl, hydroxy, C<sub>1-4</sub> alkyl, or C<sub>1-4</sub> alkoxy, preferably, methoxy, or ring A is 2,3-Dihydro-benzo[1,4]dioxin-3-yl.

[00127] In one embodiment of formula IV-A,  $R^1$  is hydrogen or methyl, and  $R^2$  is methyl, 5-methyl-pyrazol-3-yl, 5-fluoro-benzopyrazol-3-yl, or benzopyrazol-3-yl,  $X^1$ ,  $X^3$ , and  $X^4$  each is  $CH_2$ ,  $R^3$  is hydrogen or benzyl, and ring A is phenyl optionally substituted with halo, hydroxy or  $C_{1-4}$  alkoxy, preferably, methoxy.

[00128] In one embodiment of formula IV-B,  $R^1$  is hydrogen or methyl,  $R^2$  is methyl or 5-fluorobenzimidazol-3-yl, 5-methylimidazol-3-yl,  $X^1$ ,  $X^3$ , and  $X^4$  each is  $CH_2$ ,  $R^3$  is hydrogen,  $C_{1-4}$  alkyl, benzyl optionally substituted with carboxy- $C_{1-4}$  alkyl,  $C_{1-4}$  alkylsulfonyl, acyl, methylcarboxyethyl,  $C_{1-4}$  alkylcarbonyl, methoxymethylcarbonyl, or benzoyl, and ring A is phenyl substituted with 2-hydroxy, 2-trifluoromethyl, 4-methyl, 4-carboxylic acid, 4-trifluoromethyloxy, or 2- $C_{1-4}$  alkoxy, preferably, methoxy.

[00129] In one embodiment of formula IV-B,  $R^1$  is hydrogen or methyl,  $R^2$  is methyl or 5-fluorobenzimidazol-3-yl,  $X^1$ ,  $X^3$ , and  $X^4$  each is  $CH_2$ ,  $R^3$  is  $C_{1-4}$  alkyl, benzyl optionally substituted with carboxy- $C_{1-4}$  alkyl,  $C_{1-4}$  alkylsulfonyl, acyl, methylcarboxyethyl,  $C_{1-4}$  alkylcarbonyl, or benzoyl, and ring A is phenyl substituted with 2-hydroxy, 2-trifluoromethyl, or 2- $C_{1-4}$  alkoxy, preferably, methoxy.

[00130] In one embodiment of formula IV-B,  $R^1$  and  $R^2$ , each is methyl,  $X^1$ ,  $X^3$ , and  $X^4$  each is  $CH_2$ ,  $R^3$  is  $C_{1-4}$  alkyl, benzyl optionally substituted with carboxy- $C_{1-4}$  alkyl,  $C_{1-4}$  alkylsulfonyl, or benzoyl, and ring A is phenyl substituted with 2-hydroxy or 2- $C_{1-4}$  alkoxy, preferably, methoxy.

[00131] In one embodiment of formula IV-B,  $R^1$  and  $R^2$ , each is methyl,  $X^1$ ,  $X^3$ , and  $X^4$  each is  $CH_2$ ,  $R^3$  is  $C_{1-4}$  alkyl, or benzyl optionally substituted with carboxy- $C_{1-4}$  alkyl, and ring A is phenyl substituted with 2-hydroxy or 2- $C_{1-4}$  alkoxy, preferably, methoxy.

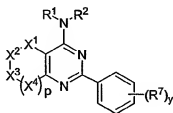
[00132] In one embodiment of formula IV-B,  $R^1$  and  $R^2$ , each is methyl,  $X^1$ ,  $X^3$ , and  $X^4$  each is  $CH_2$ ,  $R^3$  is  $C_{1-4}$  alkyl, benzyl optionally substituted with carboxy- $C_{1-4}$  alkyl,  $C_{1-4}$  alkoxy, and ring A is 2-hydroxy phenyl or 2- $C_{1-4}$  alkoxyphenyl.

[00133] In one embodiment of formula IV-B,  $R^1$  and  $R^2$ , each is methyl,  $X^1$ ,  $X^3$ , and  $X^4$  each is  $CH_2$ ,  $R^3$  is benzyl optionally substituted with carboxy- $C_{1-4}$  alkyl,  $C_{1-4}$  alkoxy, and ring A is 2-hydroxy phenyl.

[00134] In one embodiment of formula IV-M,  $R^1$  is hydrogen or methyl, and  $R^2$  is methyl, benzimidazol-3-yl, 5-methyl-imidazol-3-yl, ring A is 2-hydroxyphenyl, 2-fluorophenyl, 2-trifluoromethylphenyl or phenyl.

[00135] In one embodiment of formula IV-M,  $R^1$  is hydrogen or methyl, and  $R^2$  is methyl, benzimidazol-3-yl, 5-methyl-imidazol-3-yl, ring A is 2-trifluoromethylphenyl or phenyl.

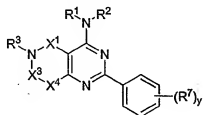
[00136] In another embodiment, Ring A is optionally substituted phenyl, and compounds of formula V are provided:



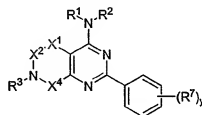
V

wherein each of  $R^1$ ,  $R^2$ ,  $X^1$ ,  $X^2$ ,  $X^3$ ,  $X^4$ ,  $R^7$ , and  $y$  are as defined generally and in subsets above and herein.

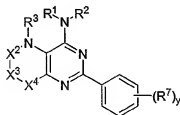
[00137] In certain preferred embodiments of formula V, one or two of  $X^1$ ,  $X^2$ ,  $X^3$ , or  $X^4$  is independently  $NR^3$ , S, C=O, O, S=O, or  $SO_2$ , and the remaining two or three are each  $CHR^4$ . In more preferred embodiments of formula V, one of  $X^1$ ,  $X^2$ ,  $X^3$ , or  $X^4$  is  $NR^3$ , S, or O, and the remaining three are each  $CHR^4$ , and compounds have one of the following structures:



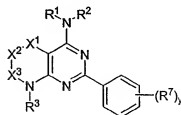
V-A



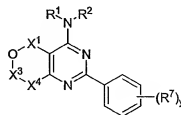
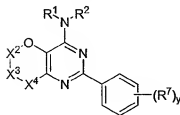
V-B

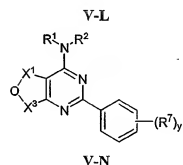
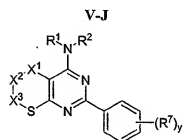
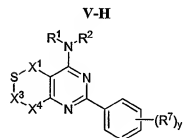
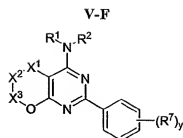
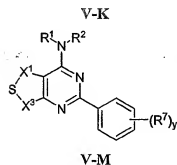
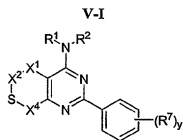
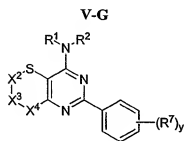
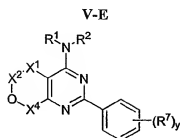


V-C



V-D





[00138] As described generally above for compounds of general formula V-A through V-N,  $R^1$  and  $R^2$  are each independently hydrogen, or an optionally substituted group selected from  $C_{1-6}$  aliphatic, a 5-6 membered aryl ring having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or  $R^1$  and  $R^2$ , taken together with the nitrogen atom to which they are bound, form an optionally substituted 3-8 membered heterocyclyl or heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein  $R^1$ ,  $R^2$ , or any ring formed by  $R^1$  and  $R^2$  taken together, are

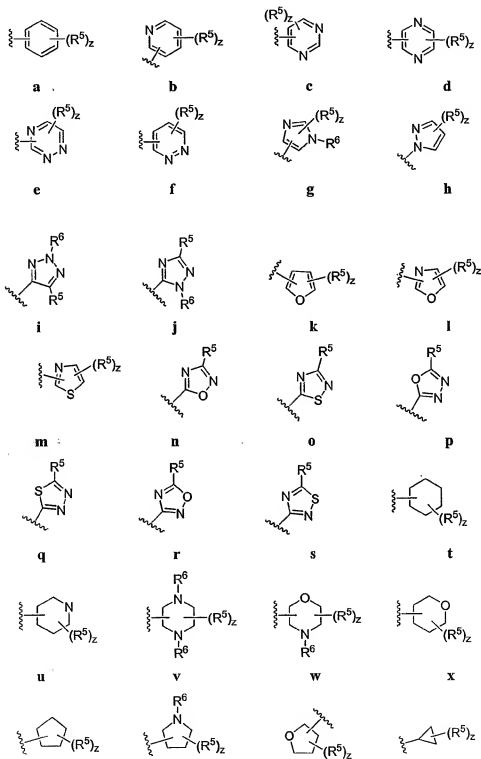
each independently optionally substituted at one or more carbon atoms with 0-4 occurrences of  $-R^5$ , and at one or more substitutable nitrogen atoms with  $-R^6$ .

[00139] In certain preferred embodiments, for compounds of any of V-A through V-N, neither  $R^1$  nor  $R^2$  is hydrogen, and  $R^1$  and  $R^2$  are each independently selected from a 5- or 6-membered aryl ring having 0-5 heteroatoms independently selected from N, O, or S, a 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from N, O, or S, or an optionally substituted  $C_{1-4}$  aliphatic group, wherein one or more methylene units in the  $C_{1-4}$  aliphatic group are optionally and independently replaced with NR, O, (CO)O, O(CO), NR(CO), (CO)NR,  $SO_2$ (NR), or (NR) $SO_2$ . In more preferred embodiments of any of formulae V-A through V-N, both  $R^1$  and  $R^2$  are an optionally substituted  $C_{1-4}$  aliphatic group, wherein one or more methylene units in the  $C_{1-4}$  aliphatic group are optionally and independently replaced with NR, O, (CO)O, O(CO), NR(CO), (CO)NR,  $SO_2$ (NR), or (NR) $SO_2$ . In yet other preferred embodiments of any of formulae V-A through V-N, when  $R^1$  and  $R^2$  are an optionally substituted  $C_{1-4}$  aliphatic group, wherein one or more methylene units in the  $C_{1-4}$  aliphatic group are optionally and independently replaced with NR, O, (CO)O, O(CO), NR(CO), (CO)NR,  $SO_2$ (NR), or (NR) $SO_2$ , preferred  $R^1$  and  $R^2$  groups are optionally substituted methyl, ethyl, cyclopropyl, n-propyl, propenyl, cyclobutyl, (CO)OCH<sub>2</sub>CH<sub>3</sub>, (CH<sub>2</sub>)<sub>2</sub>OCH<sub>3</sub>, CH<sub>2</sub>(CO)OCH<sub>2</sub>CH<sub>3</sub>, CH<sub>2</sub>(CO)OCH<sub>3</sub>, CH(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>3</sub>, or t-butyl, or n-butyl. Most preferred  $R^1$  and  $R^2$  groups of any of formulae V-A through V-N include those shown below in Table 2.

[00140] In other preferred embodiments of any of formulae V-A through V-N, one of  $R^1$  or  $R^2$  is hydrogen and the other of  $R^1$  or  $R^2$  is a 5-6 membered aryl ring having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In other embodiments of any of formulae V-A through V-N, one of  $R^1$  or  $R^2$  is hydrogen, and the other of  $R^1$  or  $R^2$  is an optionally substituted  $C_{1-4}$  aliphatic group, wherein one or more methylene units in the  $C_{1-4}$  aliphatic group are optionally and independently replaced with NR, O, (CO)O, O(CO), NR(CO), (CO)NR,  $SO_2$ (NR), or (NR) $SO_2$ .

[00141] For those embodiments described above and herein, for any of formulae V-A through V-N, where  $R^1$  or  $R^2$  is a 5- or 6-membered aryl ring having 0-5 heteroatoms independently selected from N, O, or S, or a 3-7-membered saturated or partially unsaturated ring having 0-3

heteroatoms independently selected from N, O, or S, preferred R<sup>1</sup> and R<sup>2</sup> groups are selected from:



y

z

aa

bb

wherein each  $R^5$  and  $R^6$  is as previously defined and each  $z$  is independently 0-4. Most preferred rings include those shown below in Table 2.

[00142] In still other embodiments of any of formulae V-A through V-N,  $R^1$  and  $R^2$ , taken together with the nitrogen atom to which they are bound, form an optionally substituted 3-8 membered heterocyclyl ring having 1-3 heteroatoms independently selected from nitrogen or oxygen. In certain preferred embodiments of any of formulae V-A through V-N,  $R^1$  and  $R^2$  are taken together with the nitrogen atom to which they are bound and form a 3-8 membered heterocyclyl group selected from:



cc



dd



ee



ff



gg



hh

wherein each  $R^5$  and  $R^6$  is as previously defined and each  $z$  is independently 0-4.

[00143] In other preferred embodiments of any of formulae V-A through V-N,  $R^1$  and  $R^2$  taken together are optionally substituted pyrrolidin-1-yl (ff), piperidin-1-yl (dd), piperazin-1-yl (ee), or morpholin-4-yl (ee).

[00144] As described generally above for any of formulae V-A through V-N, when  $R^1$  or  $R^2$  is a 5-6 membered aryl ring having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 3-7 membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or when  $R^1$  and  $R^2$ , taken together with the nitrogen atom to which they are bound, form an optionally substituted 3-8 membered heterocyclyl or heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, the ring can be substituted with up to four independent occurrences of  $R^5$ .

[00145] In preferred embodiments of any of formulae V-A through V-N,  $z$  is 0-2. In other preferred embodiments of any of formulae V-A through V-N,  $z$  is 0 and the ring is unsubstituted.

[00146] Preferred  $R^5$  groups of any of formulae V-A through V-N, when present, are independently halogen, CN,  $NO_2$ , or an optionally substituted group selected from  $C_{1-6}$  alkyl,

aryl, aryl(C<sub>1-6</sub>)alkyl, -N(R')<sub>2</sub>, -CH<sub>2</sub>N(R')<sub>2</sub>, OR', -CH<sub>2</sub>OR', SR', -CH<sub>2</sub>SR', COOR', -NRCOR', -(CH<sub>2</sub>)<sub>2</sub>N(R')<sub>2</sub>, -(CH<sub>2</sub>)<sub>2</sub>OR', -(CH<sub>2</sub>)<sub>2</sub>SR', -COR', -CON(R')<sub>2</sub>, SO<sub>2</sub>R', or -SO<sub>2</sub>N(R')<sub>2</sub>. In more preferred embodiments of any of formulae V-A through V-N, R<sup>5</sup> groups are each independently Cl, Br, F, CF<sub>3</sub>, Me, Et, CN, NO<sub>2</sub>, -COOH, NH<sub>2</sub>, -N(CH<sub>3</sub>)<sub>2</sub>, -N(Et)<sub>2</sub>, -N(iPr)<sub>2</sub>, -O(CH<sub>2</sub>)<sub>2</sub>OCH<sub>3</sub>, -CO(C<sub>1-4</sub>alkyl), -CONH<sub>2</sub>, -COOCH<sub>3</sub>, -OH, -CH<sub>2</sub>OH, -NHCOCH<sub>3</sub>, -SO<sub>2</sub>(C<sub>1-4</sub>alkyl), -SO<sub>2</sub>NH<sub>2</sub>, -SO<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, piperidinyl, piperizinyl, morpholino, or an optionally substituted group selected from C<sub>1-4</sub> alkoxy, phenyl, phenyloxy, benzyl, or benzyloxy. Most preferred R<sup>5</sup> groups of any of formulae V-A through V-N include those shown below in Table 2.

[00147] In preferred embodiments of any of formulae V-A through V-N R<sup>6</sup> groups are independently hydrogen, or an optionally substituted group selected from C<sub>1-6</sub> alkyl, aryl, aryl(C<sub>1-6</sub>)alkyl, -N(R')<sub>2</sub>, -CH<sub>2</sub>N(R')<sub>2</sub>, -CH<sub>2</sub>OR', -CH<sub>2</sub>SR', -(CH<sub>2</sub>)<sub>2</sub>N(R')<sub>2</sub>, -(CH<sub>2</sub>)<sub>2</sub>OR', -(CH<sub>2</sub>)<sub>2</sub>SR', -COR', -CON(R')<sub>2</sub>, SO<sub>2</sub>R', or -S(O)<sub>2</sub>N(R')<sub>2</sub>. In more preferred embodiments of any of formulae V-A through V-N, R<sup>6</sup> groups are each independently H, Me, CF<sub>3</sub>, ethyl, propyl, butyl, pentyl, CO(C<sub>1-4</sub>alkyl), -CONH<sub>2</sub>, -COO(C<sub>1-4</sub>alkyl), -CH<sub>2</sub>OH, -SO<sub>2</sub>(C<sub>1-4</sub>alkyl), -SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, or optionally substituted phenyl or benzyl. Most preferred R<sup>6</sup> groups of any of formulae V-A through V-N include those shown below in Table 2.

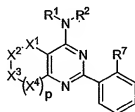
[00148] As described generally above for compounds of formula V-A through V-N, one or more of X<sup>1</sup>, X<sup>2</sup>, X<sup>3</sup>, or X<sup>4</sup> is CHR<sup>4</sup> or NR<sup>3</sup>. In preferred embodiments of any of formulae V-A through V-N, R<sup>4</sup> groups are independently hydrogen, halogen, CN, NO<sub>2</sub>, or an optionally substituted group selected from C<sub>1-6</sub> alkyl, aryl, aryl(C<sub>1-6</sub>)alkyl, -N(R')<sub>2</sub>, -CH<sub>2</sub>N(R')<sub>2</sub>, OR', -CH<sub>2</sub>OR', SR', -CH<sub>2</sub>SR', COOR', -NRCOR', -(CH<sub>2</sub>)<sub>2</sub>N(R')<sub>2</sub>, -(CH<sub>2</sub>)<sub>2</sub>OR', -(CH<sub>2</sub>)<sub>2</sub>SR', -COR', -CON(R')<sub>2</sub>, SO<sub>2</sub>R', or -SO<sub>2</sub>N(R')<sub>2</sub>. In more preferred embodiments of any of formulae V-A through V-N, R<sup>4</sup> groups are each independently H, Cl, Br, F, CF<sub>3</sub>, Me, Et, CN, NO<sub>2</sub>, -COOH, NH<sub>2</sub>, -N(CH<sub>3</sub>)<sub>2</sub>, -N(Et)<sub>2</sub>, -N(iPr)<sub>2</sub>, -O(CH<sub>2</sub>)<sub>2</sub>OCH<sub>3</sub>, -CO(C<sub>1-4</sub>alkyl), -CONH<sub>2</sub>, -COOCH<sub>3</sub>, -OH, -CH<sub>2</sub>OH, -NHCOCH<sub>3</sub>, -SO<sub>2</sub>(C<sub>1-4</sub>alkyl), -SO<sub>2</sub>NH<sub>2</sub>, -SO<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, piperidinyl, piperizinyl, morpholino, or an optionally substituted group selected from C<sub>1-4</sub> alkoxy, phenyl, phenyloxy, benzyl, or benzyloxy. Most preferred R<sup>4</sup> groups of any of formulae V-A through V-N include those shown below in Table 2.

[00149] In preferred embodiments of any of formulae V-A through V-N, R<sup>3</sup> groups are hydrogen, or an optionally substituted group selected from C<sub>1-6</sub> alkyl, aryl, aryl(C<sub>1-6</sub>)alkyl, -N(R')<sub>2</sub>, -CH<sub>2</sub>N(R')<sub>2</sub>, -CH<sub>2</sub>OR', -CH<sub>2</sub>SR', -(CH<sub>2</sub>)<sub>2</sub>N(R')<sub>2</sub>, -(CH<sub>2</sub>)<sub>2</sub>OR', -(CH<sub>2</sub>)<sub>2</sub>SR', -COR',



$-\text{CON}(\text{R}')_2$ ,  $\text{SO}_2\text{R}'$ , or  $-\text{S}(\text{O})_2\text{N}(\text{R}')_2$ . In more preferred embodiments,  $\text{R}^3$  groups are each independently H, Me,  $\text{CF}_3$ , ethyl, propyl, butyl, pentyl,  $\text{CO}(\text{C}_1\text{-C}_4\text{alkyl})$ ,  $-\text{CONH}_2$ ,  $-\text{COO}(\text{C}_1\text{-C}_4\text{alkyl})$ ,  $-\text{CH}_2\text{OH}$ ,  $-\text{SO}_2(\text{C}_1\text{-C}_4\text{alkyl})$ ,  $-\text{SO}_2\text{NH}_2$ ,  $\text{SO}_2\text{N}(\text{CH}_3)_2$ , or optionally substituted phenyl or benzyl. Most preferred  $\text{R}^3$  groups of any of formulae V-A through V-N include those shown below in Table 2.

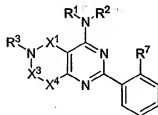
[00150] In yet other preferred embodiments of formula V y is 1 and compounds have the general formula VI:



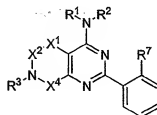
VI

wherein each of  $\text{R}^1$ ,  $\text{R}^2$ ,  $\text{X}^1$ ,  $\text{X}^2$ ,  $\text{X}^3$ ,  $\text{X}^4$ , and p is as described generally above and herein, and  $\text{R}^7$  is halogen, CN,  $\text{NO}_2$ , or an optionally substituted group selected from  $\text{C}_{1-4}$  alkyl, aryl, aralkyl,  $-\text{N}(\text{R}')_2$ ,  $-\text{CH}_2\text{N}(\text{R}')_2$ ,  $-\text{OR}'$ ,  $-\text{CH}_2\text{OR}'$ ,  $-\text{SR}'$ ,  $-\text{CH}_2\text{SR}'$ ,  $-\text{COOR}'$ ,  $-\text{NRCOR}'$ ,  $-\text{CON}(\text{R}')_2$ , or  $-\text{S}(\text{O})_2\text{N}(\text{R}')_2$ .

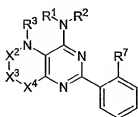
[00151] In other preferred embodiments of formula VI, p is 0, 1, or 2, and compounds have the structure of formulae VI-A through VI-N:



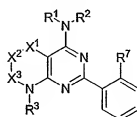
VI-A



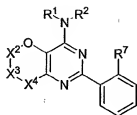
VI-B



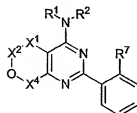
VI-C



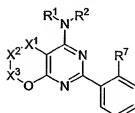
VI-D



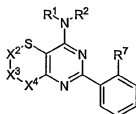
VI-E



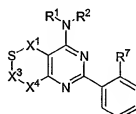
VI-F



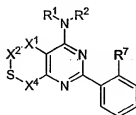
VI-G



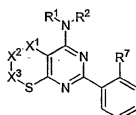
VI-H



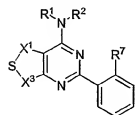
VI-I



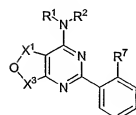
VI-J



VI-K



VI-L



VI-M

VI-N

wherein each  $R^1$ ,  $R^2$ ,  $X^1$ ,  $X^2$ ,  $X^3$ , and  $X^4$  is as described generally above and herein, and  $R^7$  is halogen, CN,  $\text{NO}_2$ , or an optionally substituted group selected from  $\text{C}_{1-4}$  alkyl, aryl, aralkyl,

$-N(R')_2$ ,  $-CH_2N(R')_2$ ,  $-OR'$ ,  $-CH_2OR'$ ,  $-SR'$ ,  $-CH_2SR'$ ,  $-COOR'$ ,  $-NRCOR'$ ,  $-CON(R')_2$ , or  $-S(O)_2N(R')_2$ .

[00152] In still other preferred embodiments compounds of the invention are defined according to any of formulae VI, VI-A, VI-B, VI-C, VI-D, VI-E, VI-F, VI-G, VI-H, VI-I, VI-J, VI-K, VI-L, VI-M, or VI-N, and one or more of, or all of,  $R^1$ ,  $R^2$ ,  $R^3$  or  $R^4$  are further defined according to one or more of, or all of, the following groups:

- $R^1$  and  $R^2$  are each independently selected from a 5- or 6-membered aryl ring having 0-5 heteroatoms independently selected from N, O, or S; a 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from N, O, or S; or an optionally substituted  $C_{1-4}$  aliphatic group, wherein one or more methylene units in the  $C_{1-4}$  aliphatic group are optionally and independently replaced with NR, O, (CO)O, O(CO), NR(CO), (CO)NR,  $SO_2(NR)$ , or  $(NR)SO_2$ ;
- each occurrence of  $R^3$  is independently hydrogen, or an optionally substituted group selected from  $C_{1-6}$  alkyl, aryl,  $aryl(C_{1-6})alkyl$ ,  $-N(R')_2$ ,  $-CH_2N(R')_2$ ,  $-CH_2OR'$ ,  $-CH_2SR'$ ,  $-(CH_2)_2N(R')_2$ ,  $-(CH_2)_2OR'$ ,  $-(CH_2)_2SR'$ ,  $-COR'$ ,  $-CON(R')_2$ ,  $SO_2R'$ , or  $-S(O)_2N(R')_2$ ; and
- each occurrence of  $R^4$  is independently hydrogen, halogen, CN,  $NO_2$ , or an optionally substituted group selected from  $C_{1-6}$  alkyl, aryl,  $aryl(C_{1-6})alkyl$ ,  $-N(R')_2$ ,  $-CH_2N(R')_2$ ,  $OR'$ ,  $-CH_2OR'$ ,  $SR'$ ,  $-CH_2SR'$ ,  $COOR'$ ,  $-NRCOR'$ ,  $-(CH_2)_2N(R')_2$ ,  $-(CH_2)_2OR'$ ,  $-(CH_2)_2SR'$ ,  $-COR'$ ,  $-CON(R')_2$ ,  $SO_2R'$ , or  $-SO_2N(R')_2$ .

[00153] In still other preferred embodiments compounds of the invention are defined according to any of formulae VI, VI-A, VI-B, VI-C, VI-D, VI-E, VI-F, VI-G, VI-H, VI-I, VI-J, VI-K, VI-L, VI-M, or VI-N, and one or more of, or all of,  $R^1$ ,  $R^2$ ,  $R^3$  or  $R^4$  are further defined according to one or more of, or all of, the following groups:

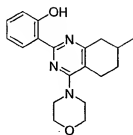
- $R^1$  and  $R^2$  are each independently optionally substituted methyl, ethyl, cyclopropyl, n-propyl, propenyl, cyclobutyl,  $(CO)OCH_2CH_3$ ,  $(CH_2)_2OCH_3$ ,  $CH_2(CO)OCH_2CH_3$ ,  $CH_2(CO)OCH_3$ ,  $CH(CH_3)CH_2CH_3$ , or t-butyl, or n-butyl;

- b. each occurrence of  $R^3$  is independently H, Me,  $CF_3$ , ethyl, propyl, butyl, pentyl,  $CO(C_1-C_4alkyl)$ ,  $-CONH_2$ ,  $-COO(C_1-C_4alkyl)$ ,  $-CH_2OH$ ,  $-SO_2(C_1-C_4alkyl)$ ,  $-SO_2NH_2$ ,  $SO_2N(CH_3)_2$ , or optionally substituted phenyl or benzyl; and
- c. each occurrence of  $R^4$  is independently H, Cl, Br, F,  $CF_3$ , Me, Et, CN,  $NO_2$ ,  $-COOH$ ,  $NH_2$ ,  $-N(CH_3)_2$ ,  $-N(Et)_2$ ,  $-N(iPr)_2$ ,  $-O(CH_2)_2OCH_3$ ,  $-CO(C_1-C_4alkyl)$ ,  $-CONH_2$ ,  $-COOCH_3$ ,  $-OH$ ,  $-CH_2OH$ ,  $-NHCOCH_3$ ,  $-SO_2(C_1-C_4alkyl)$ ,  $-SO_2NH_2$ ,  $-SO_2N(CH_3)_2$ , piperidinyl, piperizinyl, morpholino, or an optionally substituted group selected from  $C_{1-4}$  alkoxy, phenyl, phenyloxy, benzyl, or benzyloxy.

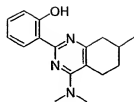
[00154] In still other preferred embodiments compounds of the invention are defined according to any of formulae VI, VI-A, VI-B, VI-C, VI-D, VI-E, VI-F, VI-G, VI-H, VI-I, VI-J, VI-K, VI-L, VI-M, or VI-N, and one or more of, or all of,  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$  or  $R^7$  are further defined according to one or more of, or all of, the following groups:

- a.  $R^1$  and  $R^2$  are each independently optionally substituted methyl, ethyl, cyclopropyl, n-propyl, propenyl, cyclobutyl,  $(CO)OCH_2CH_3$ ,  $(CH_2)_2OCH_3$ ,  $CH_2(CO)OCH_2CH_3$ ,  $CH_2(CO)OCH_3$ ,  $CH(CH_3)CH_2CH_3$ , or t-butyl, or n-butyl;
- b. each occurrence of  $R^3$  is independently H, Me,  $CF_3$ , ethyl, propyl, butyl, pentyl,  $CO(C_1-C_4alkyl)$ ,  $-CONH_2$ ,  $-COO(C_1-C_4alkyl)$ ,  $-CH_2OH$ ,  $-SO_2(C_1-C_4alkyl)$ ,  $-SO_2NH_2$ ,  $SO_2N(CH_3)_2$ , or optionally substituted phenyl or benzyl;
- c. each occurrence of  $R^4$  is independently H, Cl, Br, F,  $CF_3$ , Me, Et, CN,  $NO_2$ ,  $-COOH$ ,  $NH_2$ ,  $-N(CH_3)_2$ ,  $-N(Et)_2$ ,  $-N(iPr)_2$ ,  $-O(CH_2)_2OCH_3$ ,  $-CO(C_1-C_4alkyl)$ ,  $-CONH_2$ ,  $-COOCH_3$ ,  $-OH$ ,  $-CH_2OH$ ,  $-NHCOCH_3$ ,  $-SO_2(C_1-C_4alkyl)$ ,  $-SO_2NH_2$ ,  $-SO_2N(CH_3)_2$ , piperidinyl, piperizinyl, morpholino, or an optionally substituted group selected from  $C_{1-4}$  alkoxy, phenyl, phenyloxy, benzyl, or benzyloxy; and
- d.  $R^7$  is Cl, Br, F,  $CF_3$ , Me, Et, CN,  $NO_2$ ,  $-COOH$ ,  $NH_2$ ,  $-N(CH_3)_2$ ,  $-N(Et)_2$ ,  $-N(iPr)_2$ ,  $-O(CH_2)_2OCH_3$ ,  $-CO(C_1-C_4alkyl)$ ,  $-CONH_2$ ,  $-COOCH_3$ ,  $-OH$ ,  $-CH_2OH$ ,  $-NHCOCH_3$ ,  $-SO_2(C_1-C_4alkyl)$ ,  $-SO_2NH_2$ ,  $-SO_2N(CH_3)_2$ , piperidinyl, piperizinyl, morpholino, or an optionally substituted group selected from  $C_{1-4}$  alkoxy, phenyl, phenyloxy, benzyl, or benzyloxy.

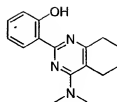
[00155] Representative examples of compounds as described above and herein are set forth below and in Table 2.



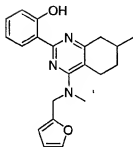
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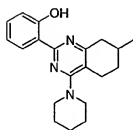
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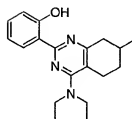
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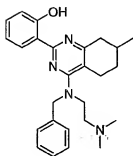
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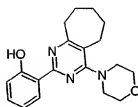
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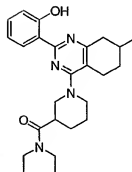
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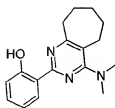
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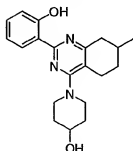
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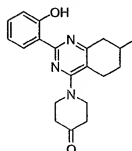
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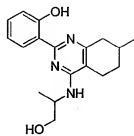
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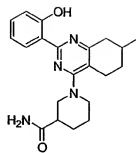
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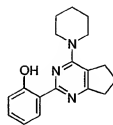
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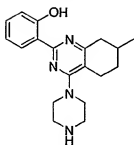
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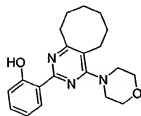
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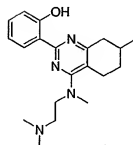
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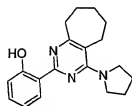
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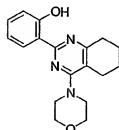
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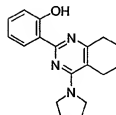
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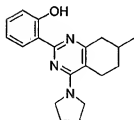
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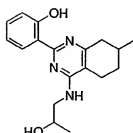
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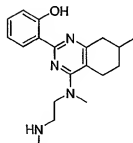
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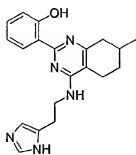
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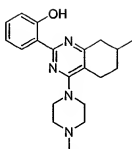
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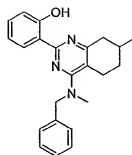
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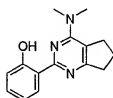
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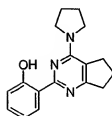
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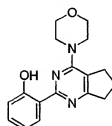
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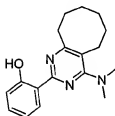
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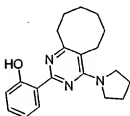
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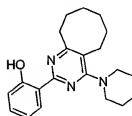
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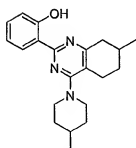
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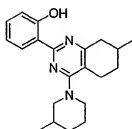
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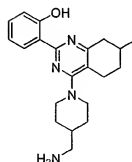
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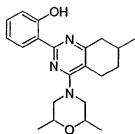
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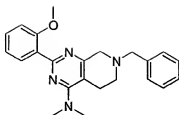
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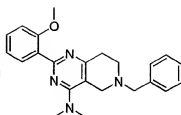
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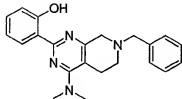
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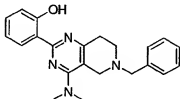
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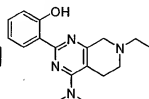
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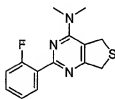
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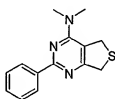
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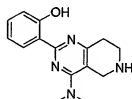
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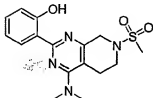
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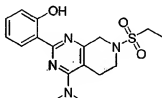
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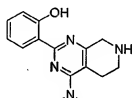
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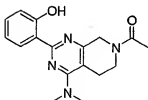
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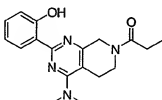
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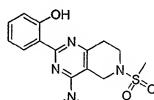
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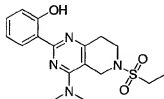
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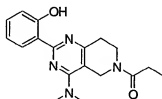
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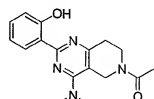
I-51



[00156] I-52



I-53

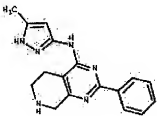
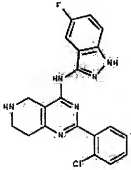
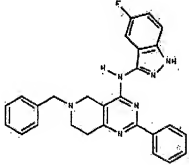
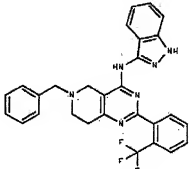
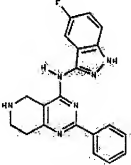
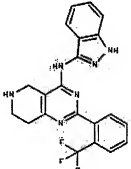
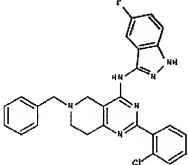
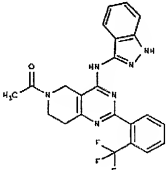


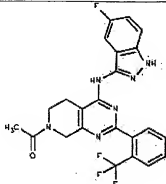
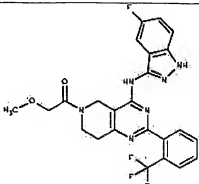
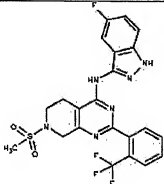
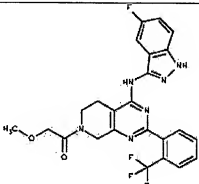
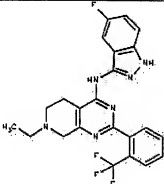
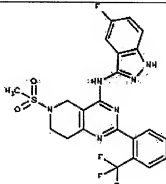
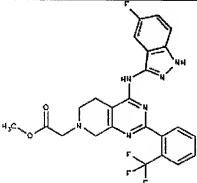
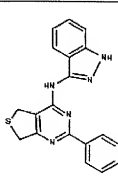
or I-54.

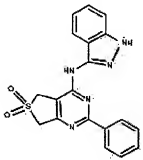
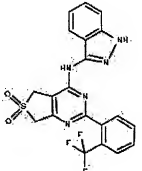
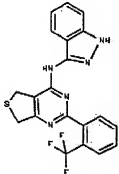
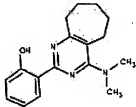
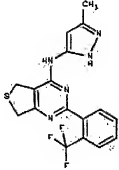
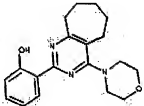
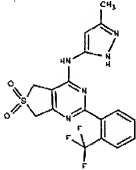
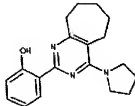


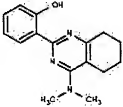
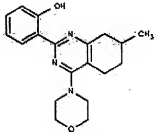
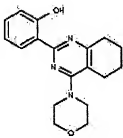
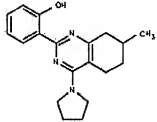
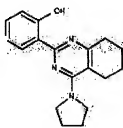
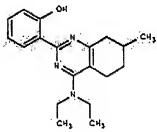
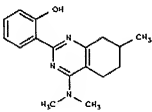
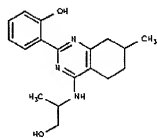
[00157] Table 2. Examples of Compounds of Formula 1:

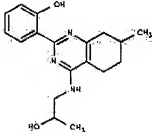
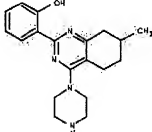
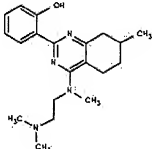
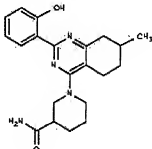
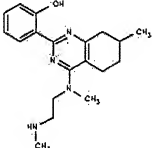
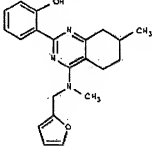
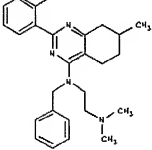
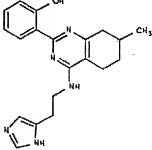
Cmpd	Structure	Cmpd	Structure
1		5	
2		6	
3		7	
4		8	

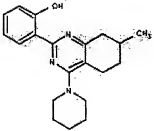
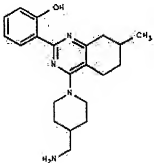
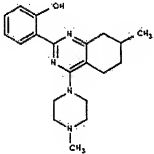
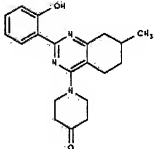
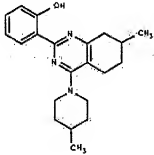
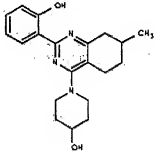
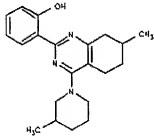
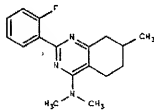
Cmpd	Structure	Cmpd	Structure
9		13	
10		14	
11		15	
12		16	

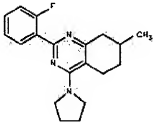
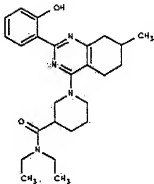
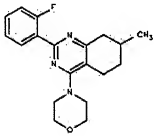
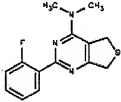
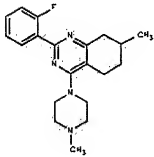
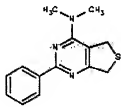
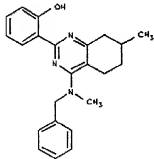
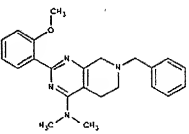
Cmpd	Structure	Cmpd	Structure
17		21	
18		22	
19		23	
20		24	

Cmpd	Structure	Cmpd	Structure
25		29	
26		30	
27		31	
28		32	

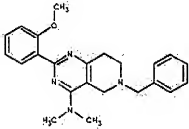
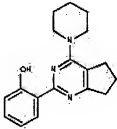
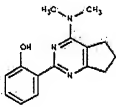
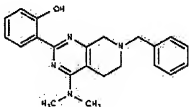
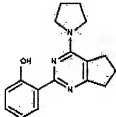
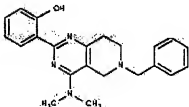
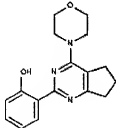
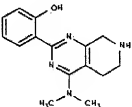
Cmpd	Structure	Cmpd	Structure
33		37	
34		38	
35		39	
36		40	

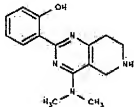
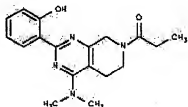
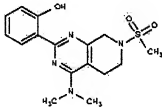
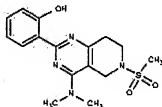
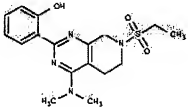
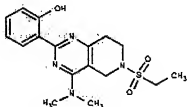
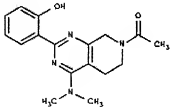
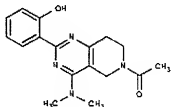
Cmpd	Structure	Cmpd	Structure
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42		46	
43		47	
44		48	

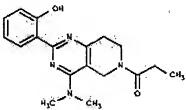
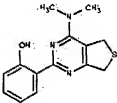
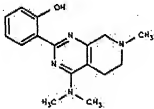
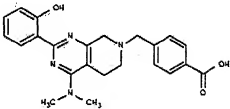
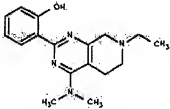
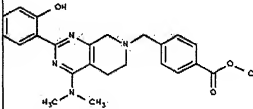
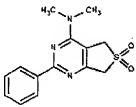
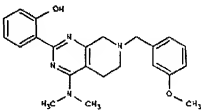
Cmpd	Structure	Cmpd	Structure
49		53	
50		54	
51		55	
52		56	

Cmpd	Structure	Cmpd	Structure
57		61	
58		62	
59		63	
60		64	

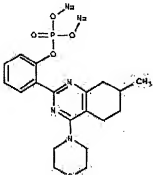
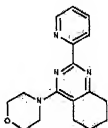
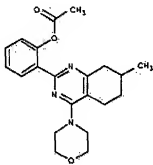
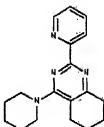
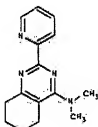
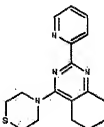
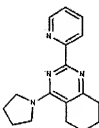
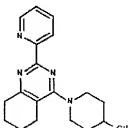


Cmpd	Structure	Cmpd	Structure
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66		70	
67		71	
68		72	

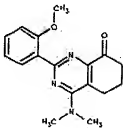
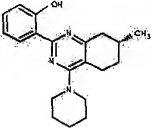
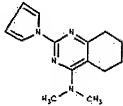
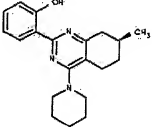
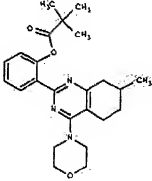
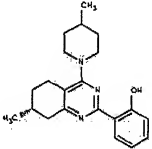
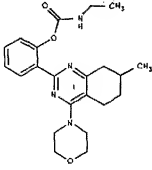
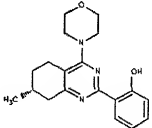
Cmpd	Structure	Cmpd	Structure
73		77	
74		78	
75		79	
76		80	

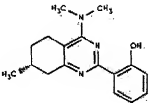
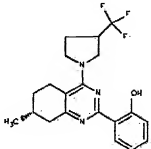
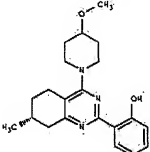
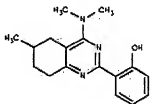
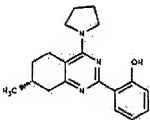
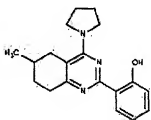
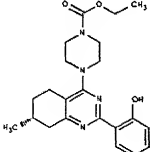
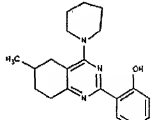
Cmpd	Structure	Cmpd	Structure
81		85	
82		86	
83		87	
84		88	

Cmpd	Structure	Cmpd	Structure
89		93	
90		94	
91		95	
92		96	

Cmpd	Structure	Cmpd	Structure
97		101	
98		102	
99		103	
100		104	

Cmpd	Structure	Cmpd	Structure
105	 <chem>CN(C)c1nc2c(ncn2C3CCCCC3)c4cccnc4</chem>	109	 <chem>C1CCSCC1n2c3c(ncn3C4CCCCC4)c5cccnc52</chem>
106	 <chem>C1CCCN1n2c3c(ncn3C4CCCCC4)c5cccnc52</chem>	110	 <chem>OC1CCCCC1Nc2nc3c(ncn3C4CCCCC4)c5cccnc52</chem>
107	 <chem>C1CCOCC1n2c3c(ncn3C4CCCCC4)c5cccnc52</chem>	111	 <chem>CC1CCNCC1Nc2nc3c(ncn3C4CCCCC4)c5cccnc52</chem>
108	 <chem>C1CCNCC1n2c3c(ncn3C4CCCCC4)c5cccnc52</chem>	112	 <chem>CN(C)C1CCCCC1Nc2nc3c(ncn3C4CCCCC4)c5cccnc52C(=O)OC6=CC=CC=C6</chem>

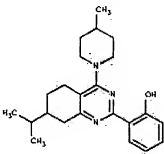
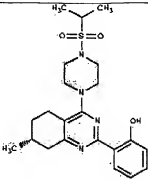
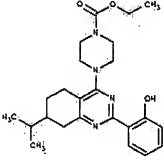
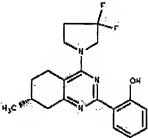
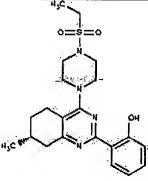
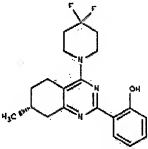
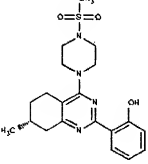
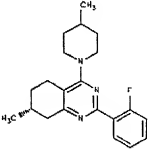
Cmpd	Structure	Cmpd	Structure
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114		118	
115		119	
116		120	

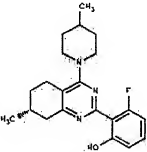
Cmpd	Structure	Cmpd	Structure
121		125	
122		126	
123		127	
124		128	



Cmpd	Structure
129	
130	
131	
132	

Cmpd	Structure
133	
134	
135	
136	

Cmpd	Structure	Cmpd	Structure
137		141	
138		142	
139		143	
140		144	

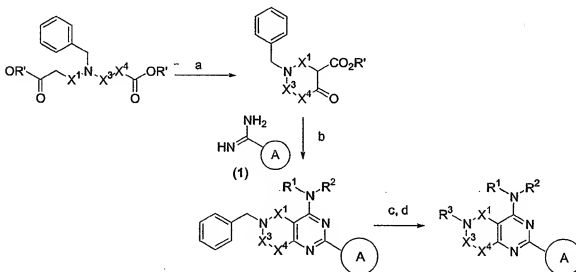
Cmpd	Structure
145	 <p>The chemical structure of compound 145 is a complex molecule. It features a central pyrimidine ring system. Attached to this system is a cyclohexyl group with a methyl group (CH<sub>3</sub>) at the 1-position. Another attachment is a 2-fluoro-3-chlorophenyl group. The structure is drawn with stereochemical indicators (wedges and dashes) at the points of attachment to the cyclohexyl ring.</p>

[00158] 4. *General Synthetic Methodology:*

[00159] The compounds of this invention may be prepared in general by methods known to those skilled in the art for analogous compounds, as illustrated by the general scheme below, and the preparative examples that follow.

[00160] As described in more detail in the Examples herein, and as shown generally in Scheme A below, reaction of a desired heterocyclohexanone-1-carboxylate and an amidine in ethanol with NaOEt at 0°C, and subsequent reaction with phosphorus oxychloride, boron tribromide and a desired amine, followed by debenzoylation and reaction with an appropriate chloride generates compounds of general formula I'.

**Scheme A: Preparation of C6\_Aza\_6 and Elaboration**

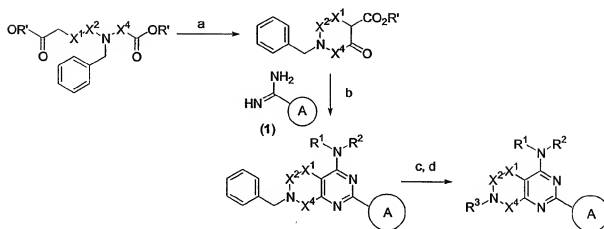


[00161] Conditions: a) i. SnCl<sub>4</sub>, CH<sub>2</sub>Cl<sub>2</sub>; ii. Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>; b) i. 1, NaOEt, EtOH; ii. POCl<sub>3</sub>, N,N-dimethylaniline, benzene, reflux; iii. R<sup>1</sup>R<sup>2</sup>NH, THF/CH<sub>2</sub>Cl<sub>2</sub>, RT; c) Pd/C, H<sub>2</sub>, AcOH, 90 °C; d) R<sup>3</sup>-Cl, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>.

[00162] It will be appreciated that this method can be utilized to prepare a variety of compounds.

[00163] Scheme B below depicts the preparation of C7\_Aza\_6 compounds and elaboration:

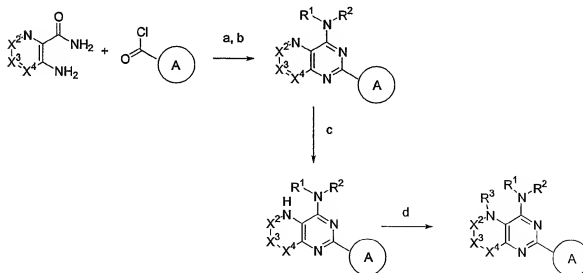
## Scheme B: Preparation of C7\_Aza\_6 and Elaboration



[00164] Conditions: a) i.  $\text{SnCl}_4$ ,  $\text{CH}_2\text{Cl}_2$ ; ii.  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ ; b) i. 1,  $\text{NaOEt}$ ,  $\text{EtOH}$ ; ii.  $\text{POCl}_3$ ,  $\text{N,N}$ -dimethylaniline, benzene, reflux; iii.  $\text{R}^1\text{R}^2\text{NH}$ ,  $\text{THF}/\text{CH}_2\text{Cl}_2$ , RT; c)  $\text{Pd/C}$ ,  $\text{H}_2$ ,  $\text{AcOH}$ ,  $90^\circ\text{C}$ ; d)  $\text{R}^3\text{-Cl}$ ,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ .

[00165] Scheme C below depicts the preparation of C5\_Aza\_6 compounds:

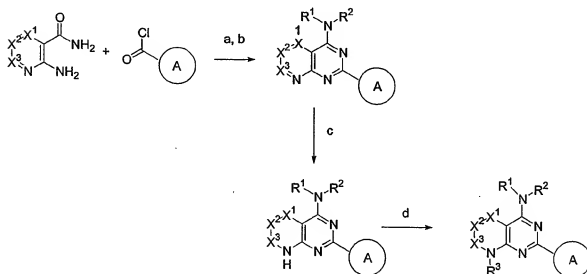
## Scheme C: Preparation of C5\_Aza\_6 and Elaborations



[00166] **Conditions:** a) i. Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>; ii. NaOH, H<sub>2</sub>O, reflux b) i. POCl<sub>3</sub>, N,N-dimethylaniline, benzene, reflux; ii. R<sup>1</sup>R<sup>2</sup>NH, THF/CH<sub>2</sub>Cl<sub>2</sub>, RT; c) H<sub>2</sub>, Pt<sub>2</sub>O<sub>2</sub>, TFA, EtOH; d) R<sup>3</sup>-Cl, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>.

[00167] Scheme D below depicts the preparation of C8\_Aza\_6 compounds and elaborations:

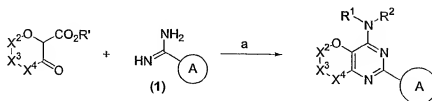
**Scheme D: Preparation of C8-Aza\_6 and Elaborations**



[00168] **Conditions:** a) i. Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>; ii. NaOH, H<sub>2</sub>O, reflux b) i. POCl<sub>3</sub>, N,N-dimethylaniline, benzene, reflux; ii. R<sup>1</sup>R<sup>2</sup>NH, THF/CH<sub>2</sub>Cl<sub>2</sub>, RT; c) H<sub>2</sub>, Pt<sub>2</sub>O<sub>2</sub>, TFA, EtOH; d) R<sup>3</sup>-Cl, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>.

[00169] Scheme E below depicts the preparation of C5\_Oxa\_6 compounds:

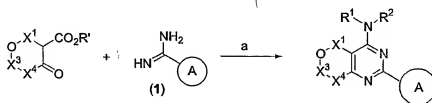
**Scheme E: C5\_Oxa\_6 compounds**



[00170] Conditions: a) i. 1, NaOEt, EtOH, reflux; ii. POCl<sub>3</sub>, N,N-dimethylaniline, benzene, reflux; ii. R<sup>1</sup>R<sup>2</sup>NH, THF/CH<sub>2</sub>Cl<sub>2</sub>, RT.

[00171] Scheme F below depicts the preparation of C6\_Oxa\_6 compounds:

**Scheme F: C6\_Oxa\_6 compounds**

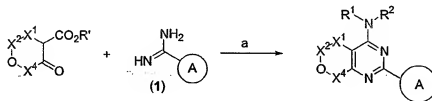


[00172] Conditions: a) i. 1, NaOEt, EtOH, reflux; ii. POCl<sub>3</sub>, N,N-dimethylaniline, benzene, reflux; ii. R<sup>1</sup>R<sup>2</sup>NH, THF/CH<sub>2</sub>Cl<sub>2</sub>, RT.

[00173] Scheme G below depicts the preparation of C7\_Oxa\_6 compounds:

[00174]

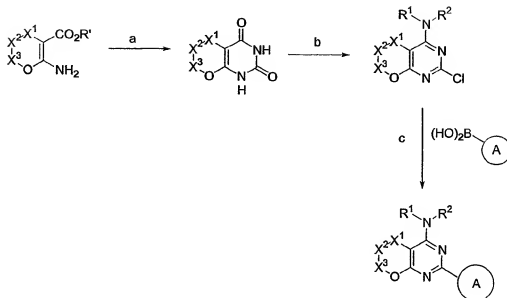
**Scheme G: C7\_Oxa\_6 compounds**



[00175] Conditions: a) i. 1, NaOEt, EtOH, reflux; ii. POCl<sub>3</sub>, N,N-dimethylaniline, benzene, reflux; ii. R<sup>1</sup>R<sup>2</sup>NH, THF/CH<sub>2</sub>Cl<sub>2</sub>, RT.

[00176] Scheme H below depicts the preparation of C8\_Oxa\_6 compounds:

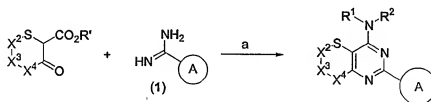
## Scheme H: C8\_Oxa\_6 compounds



[00177] Conditions: a) i. ClSO<sub>2</sub>NCO, CH<sub>2</sub>Cl<sub>2</sub>; ii. KOH, H<sub>2</sub>O; b) i. POCl<sub>3</sub>, N,N-dimethylaniline, benzene, reflux; ii. R<sup>1</sup>R<sup>2</sup>NH, THF/CH<sub>2</sub>Cl<sub>2</sub>, RT; c) Pd(Ph<sub>3</sub>)<sub>4</sub>, Na<sub>2</sub>CO<sub>3</sub>, CH<sub>3</sub>CN, H<sub>2</sub>O, reflux

[00178] Scheme I below depicts the preparation of C5\_thia\_6 compounds:

## Scheme I: C5\_Thia\_6 compounds

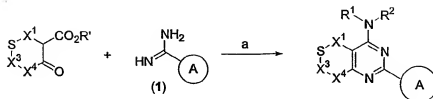


[00179] Conditions: a) i. 1, NaOEt, EtOH, reflux; ii. POCl<sub>3</sub>, N,N-dimethylaniline, benzene, reflux; ii. R<sup>1</sup>R<sup>2</sup>NH, THF/CH<sub>2</sub>Cl<sub>2</sub>, RT.

[00180] Scheme J below depicts the preparation of C6\_Thia\_6 compounds:

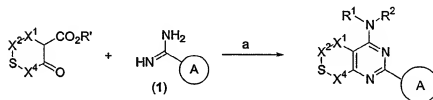


## Scheme J: C6\_Thia\_6 compounds



[00181] Scheme K below depicts the preparation of C7\_Thia\_6 compounds:

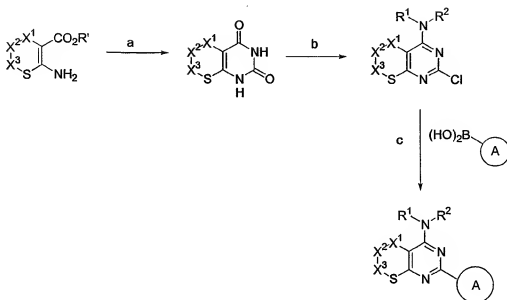
## Scheme K: C7\_Thia\_6 compounds



[00182] Conditions: a) i. 1, NaOEt, EtOH, reflux; ii. POCl<sub>3</sub>, N,N-dimethylaniline, benzene, reflux; ii. R<sup>1</sup>R<sup>2</sup>NH, THF/CH<sub>2</sub>Cl<sub>2</sub>, RT.

[00183] Scheme L below depicts the preparation of C8\_Thia\_6 compounds:

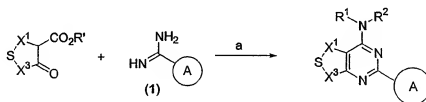
## Scheme L: C8\_Thia\_6 compounds



[00184] Conditions: a) i.  $\text{ClSO}_2\text{NCO}$ ,  $\text{CH}_2\text{Cl}_2$ ; ii.  $\text{KOH}$ ,  $\text{H}_2\text{O}$ ; b) i.  $\text{POCl}_3$ ,  $N,N$ -dimethylaniline, benzene, reflux; ii.  $\text{R}^1\text{R}^2\text{NH}$ ,  $\text{THF}/\text{CH}_2\text{Cl}_2$ , RT; c)  $\text{Pd}(\text{Ph}_3)_4$ ,  $\text{Na}_2\text{CO}_3$ ,  $\text{CH}_3\text{CN}$ ,  $\text{H}_2\text{O}$ , reflux

[00185] Scheme M below depicts the preparation of C6\_thia\_5 compounds:

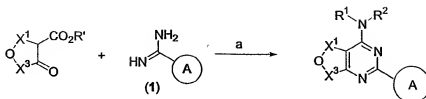
## Scheme M: C6\_Thia\_5 compounds



[00186] Conditions: a) i. 1,  $\text{NaOEt}$ ,  $\text{EtOH}$ , reflux; ii.  $\text{POCl}_3$ ,  $N,N$ -dimethylaniline, benzene, reflux; ii.  $\text{R}^1\text{R}^2\text{NH}$ ,  $\text{THF}/\text{CH}_2\text{Cl}_2$ , RT.

[00187] Scheme N below depicts the preparation of C6\_oxa\_5 compounds:

## Scheme N: C6\_oxa\_5 compounds

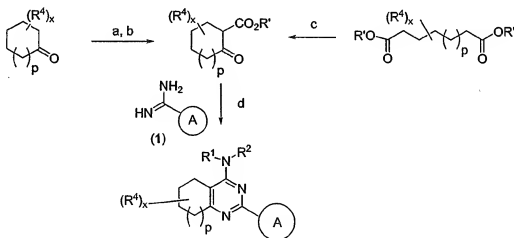


[00188] Conditions: a) i. 1, NaOEt, EtOH, reflux; ii. POCl<sub>3</sub>, N,N-dimethylaniline, benzene, reflux; iii. R<sup>1</sup>R<sup>2</sup>NH, THF/CH<sub>2</sub>Cl<sub>2</sub>, RT.

[00189]

[00190] As described in more detail in the Examples herein, and as shown generally in Scheme O below, reaction of a desired cyclohexanone-1-carboxylate and an amidine in ethanol with NaOEt at 0°C, and subsequent reaction with phosphorus oxychloride, boron tribromide, and a desired amine generates compounds of general formula I'.

## Scheme O: Preparation of β-Ketoesters and Elaboration

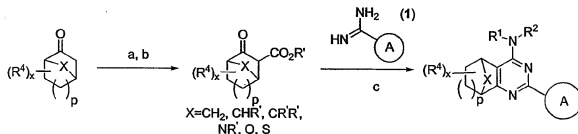


[00191] Conditions: a) LDA, R'OC(O)CN, THF; b) NaOR', R'OH, 48h, rt; c) NaOR', R'OH; d) i. 1, NaOEt, EtOH; ii. POCl<sub>3</sub>, N,N-dimethylaniline, benzene, reflux; iii. R<sup>1</sup>R<sup>2</sup>NH, THF/CH<sub>2</sub>Cl<sub>2</sub>, RT.

[00192] It will be appreciated that this method can be utilized to prepare a variety of compounds.

[00193] Scheme P below depicts the preparation of bicyclic  $\beta$ -ketoesters:

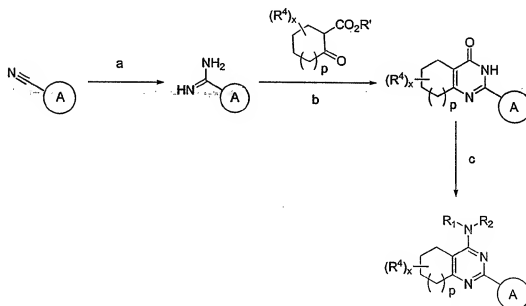
**Scheme P: Preparation of Bicyclic  $\beta$ -Ketoesters and Elaboration**



[00194] Conditions: a) i. LDA,  $R'OC(O)CN$ , THF; ii. b)  $NaOR'$ ,  $R'OH$ , 48h, rt; c) i.  $NaOEt$ ,  $EtOH$ ; ii.  $POCl_3$ ,  $N,N$ -dimethylaniline, benzene, reflux; iii.  $R^1R^2NH$ ,  $THF/CH_2Cl_2$ , RT.

[00195] Additional conditions for the preparation of compounds of formula I' and subsets thereof is presnted below in Scheme Q.

**Scheme Q: Additional Amidine Syntheses and Elaborations**

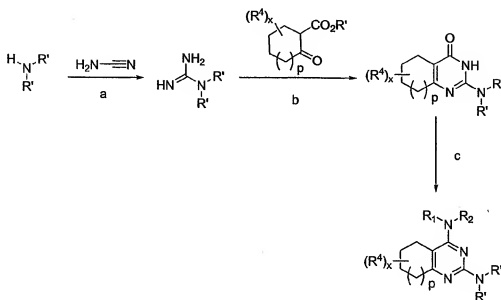


[00196] Conditions: a) i.  $LiHMDS$ ; ii.  $HCl$  or i.  $HCl$ ,  $MeOH$ ; ii.  $NH_3$ ; b)  $NaOEt$ ,  $EtOH$ ; c) i.  $POCl_3$ ,  $N,N$ -dimethylaniline, benzene, reflux; ii.  $R^1R^2NH$ ,  $THF/CH_2Cl_2$ , RT.

[00197] In certain other embodiments, Ring A represents an N-linked heteroaryl or heterocyclyl group (as depicted below in Scheme R, where two occurrences of  $R'$  are taken

together below to form an optionally substituted 5-8-membered cycloalkyl, heterocycl, aryl, or heteoaryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur).

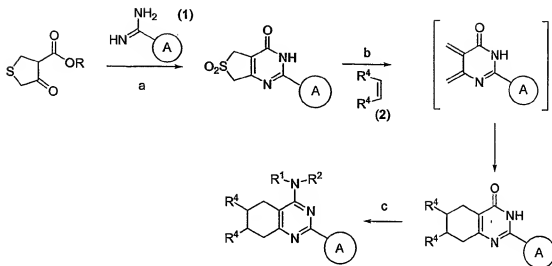
**Scheme R: Amidine Synthesis and Elaboration: C2 Aza**



[00198] Conditions: a)  $\text{H}_2\text{O}$ ; b)  $\text{NaOEt}$ ,  $\text{EtOH}$ ; c) i.  $\text{POCl}_3$ ,  $N,N$ -dimethylaniline, benzene, reflux; ii.  $\text{R}^1\text{R}^2\text{NH}$ ,  $\text{THF}/\text{CH}_2\text{Cl}_2$ , RT.

[00199] In still other embodiments, compounds of the invention are prepared via Diels-Alder reactions to provide substituted tetrahydroquinazoline moieties as depicted in Scheme S below:

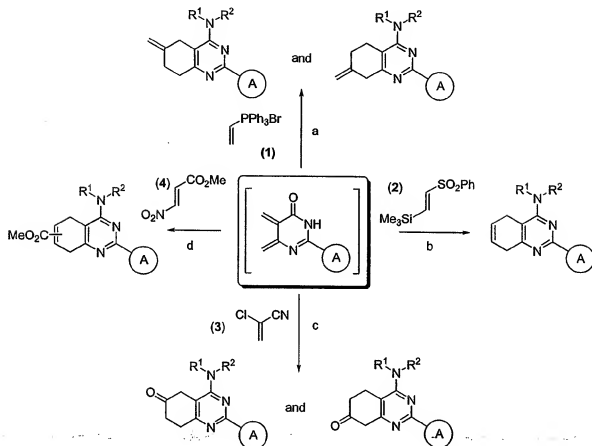
## Scheme S: Diels-Alder Reactions



[00200] Conditions: a) i. 1, EtOH; ii. m-CPBA; b) 2, toluene, reflux, 18 h; c) i. POCl<sub>3</sub>, N,N-dimethylaniline, benzene, reflux; ii. R<sup>1</sup>R<sup>2</sup>NH, THF/CH<sub>2</sub>Cl<sub>2</sub>, RT.

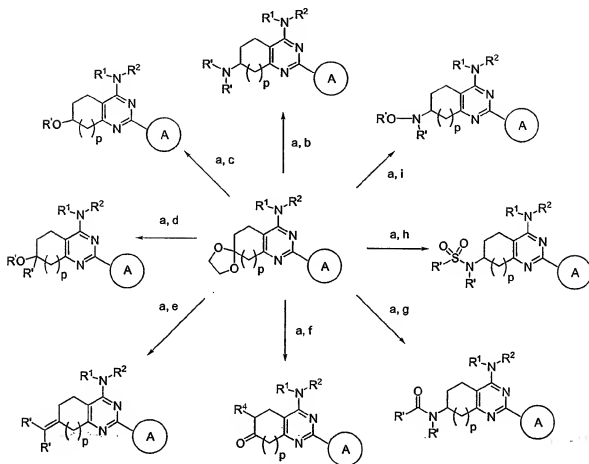
[00201] Further functionalization of inventive compounds can be achieved via exemplary reactions as depicted below in Schemes T and U:

## Scheme T: Additional Diels Alder Reactions



[00202] **Conditions:** a) i. 1; ii. LDA, HCHO; iii.  $\text{POCl}_3$ ; iv.  $\text{R}^1\text{R}^2\text{NH}$ ; b) i. 2; ii. TBAF; iii.  $\text{POCl}_3$ ; iv.  $\text{R}^1\text{R}^2\text{NH}$ ; c) i. 3; ii.  $\text{Na}_2\text{S}$ ; iii.  $\text{POCl}_3$ ; iv.  $\text{R}^1\text{R}^2\text{NH}$ ; d) i. 4; ii. DBU; iii.  $\text{POCl}_3$ ; iv.  $\text{R}^1\text{R}^2\text{NH}$ .

## Scheme U: Cycloalkanoyl Derivatization



[00203] Conditions: a) 25% H<sub>2</sub>SO<sub>4</sub>; b) NaBH(OAc)<sub>3</sub>, AcOH, R'R'NH, DCE, rt; c) i. NaBH<sub>4</sub>, MeOH; ii. NaH, R'X; d) i. R'MgBr; ii. R'X; e) R'R'C=P(Ph)<sub>3</sub>; f) LDA, R'X; g) i. R'NH<sub>2</sub>, NaBH(OAc)<sub>3</sub>, AcOH; ii. pyridine, R'C(O)Cl; h) i. R'NH<sub>2</sub>, NaBH(OAc)<sub>3</sub>, AcOH; ii. pyridine, R'SO<sub>2</sub>Cl; i) NH<sub>2</sub>OR', TsOH.

[00204] Although certain exemplary embodiments are depicted and described above and herein, it will be appreciated that a compounds of the invention can be prepared according to the methods described generally above using appropriate starting materials by methods generally available to one of ordinary skill in the art.



**[00205]** 5. *Uses, Formulation and Administration*

**[00206]** *Pharmaceutically acceptable compositions*

**[00207]** As discussed above, the present invention provides compounds that are inhibitors of voltage-gated sodium ion channels, and thus the present compounds are useful for the treatment of diseases, disorders, and conditions including, but not limited to acute, chronic, neuropathic, or inflammatory pain, arthritis, migraine, cluster headaches, trigeminal neuralgia, herpetic neuralgia, general neuralgias, epilepsy or epilepsy conditions, neurodegenerative disorders, psychiatric disorders such as anxiety and depression, myotonia, arrhythmia, movement disorders, neuroendocrine disorders, ataxia, multiple sclerosis, irritable bowel syndrome, and incontinence. Accordingly, in another aspect of the present invention, pharmaceutically acceptable compositions are provided, wherein these compositions comprise any of the compounds as described herein, and optionally comprise a pharmaceutically acceptable carrier, adjuvant or vehicle. In certain embodiments, these compositions optionally further comprise one or more additional therapeutic agents.

**[00208]** It will also be appreciated that certain of the compounds of present invention can exist in free form for treatment, or where appropriate, as a pharmaceutically acceptable derivative thereof. According to the present invention, a pharmaceutically acceptable derivative includes, but is not limited to, pharmaceutically acceptable salts, esters, salts of such esters, or any other adduct or derivative which upon administration to a patient in need is capable of providing, directly or indirectly, a compound as otherwise described herein, or a metabolite or residue thereof.

**[00209]** As used herein, the term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgement, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. A "pharmaceutically acceptable salt" means any non-toxic salt or salt of an ester of a compound of this invention that, upon administration to a recipient, is capable of providing, either directly or indirectly, a compound of this invention or an inhibitorily active metabolite or residue thereof. As used herein, the term "inhibitorily active metabolite or residue thereof" means that a metabolite or residue thereof is also an inhibitor of a voltage-gated sodium ion channel.

[00210] Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge, *et al.* describe pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences*, 1977, 66, 1-19, incorporated herein by reference. Pharmaceutically acceptable salts of the compounds of this invention include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like. Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and  $N^+(C_{1-4}alkyl)_4$  salts. This invention also envisions the quaternization of any basic nitrogen-containing groups of the compounds disclosed herein. Water or oil-soluble or dispersible products may be obtained by such quaternization. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, loweralkyl sulfonate and aryl sulfonate.

[00211] As described above, the pharmaceutically acceptable compositions of the present invention additionally comprise a pharmaceutically acceptable carrier, adjuvant, or vehicle, which, as used herein, includes any and all solvents, diluents, or other liquid vehicle, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, solid binders, lubricants and the like, as suited to the particular dosage form desired. Remington's Pharmaceutical Sciences, Sixteenth Edition, E. W. Martin (Mack

Publishing Co., Easton, Pa., 1980) discloses various carriers used in formulating pharmaceutically acceptable compositions and known techniques for the preparation thereof. Except insofar as any conventional carrier medium is incompatible with the compounds of the invention, such as by producing any undesirable biological effect or otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutically acceptable composition, its use is contemplated to be within the scope of this invention. Some examples of materials which can serve as pharmaceutically acceptable carriers include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, or potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, wool fat, sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil; safflower oil; sesame oil; olive oil; corn oil and soybean oil; glycols; such as propylene glycol or polyethylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator.

**[00212]** *Uses of Compounds and Pharmaceutically Acceptable Compositions*

**[00213]** In yet another aspect, a method for the treatment or lessening the severity of acute, chronic, neuropathic, or inflammatory pain, arthritis, migraine, cluster headaches, trigeminal neuralgia, herpetic neuralgia, general neuralgias, epilepsy or epilepsy conditions, neurodegenerative disorders, psychiatric disorders such as anxiety and depression, myotonia, arrhythmia, movement disorders, neuroendocrine disorders, ataxia, multiple sclerosis, irritable

bowel syndrome, or incontinence is provided comprising administering an effective amount of a compound, or a pharmaceutically acceptable composition comprising a compound to a subject in need thereof. In certain preferred embodiments, a method for the treatment or lessening the severity of acute, chronic, neuropathic, or inflammatory pain is provided comprising administering an effective amount of a compound or a pharmaceutically acceptable composition to a subject in need thereof. In certain embodiments of the present invention an "effective amount" of the compound or pharmaceutically acceptable composition is that amount effective for treating or lessening the severity of one or more of acute, chronic, neuropathic, or inflammatory pain, epilepsy or epilepsy conditions, neurodegenerative disorders, psychiatric disorders such as anxiety and depression, myotonia, arrhythmia, movement disorders, neuroendocrine disorders, ataxia, multiple sclerosis, irritable bowel syndrome, or incontinence.

[00214] The compounds and compositions, according to the method of the present invention, may be administered using any amount and any route of administration effective for treating or lessening the severity of one or more of acute, chronic, neuropathic, or inflammatory pain, epilepsy or epilepsy conditions, neurodegenerative disorders, psychiatric disorders such as anxiety and depression, myotonia, arrhythmia, movement disorders, neuroendocrine disorders, ataxia, multiple sclerosis, irritable bowel syndrome, or incontinence. The exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the infection, the particular agent, its mode of administration, and the like. The compounds of the invention are preferably formulated in dosage unit form for ease of administration and uniformity of dosage. The expression "dosage unit form" as used herein refers to a physically discrete unit of agent appropriate for the patient to be treated. It will be understood, however, that the total daily usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific effective dose level for any particular patient or organism will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed, and

like factors well known in the medical arts. The term "patient", as used herein, means an animal, preferably a mammal, and most preferably a human.

[00215] The pharmaceutically acceptable compositions of this invention can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), buccally, as an oral or nasal spray, or the like, depending on the severity of the infection being treated. In certain embodiments, the compounds of the invention may be administered orally or parenterally at dosage levels of about 0.01 mg/kg to about 50 mg/kg and preferably from about 1 mg/kg to about 25 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic effect.

[00216] Liquid dosage forms for oral administration include, but are not limited to, pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

[00217] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

[00218] The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid

compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

**[00219]** In order to prolong the effect of a compound of the present invention, it is often desirable to slow the absorption of the compound from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the compound then depends upon its rate of dissolution that, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered compound form is accomplished by dissolving or suspending the compound in an oil vehicle. Injectable depot forms are made by forming microencapsule matrices of the compound in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of compound to polymer and the nature of the particular polymer employed, the rate of compound release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the compound in liposomes or microemulsions that are compatible with body tissues.

**[00220]** Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

**[00221]** Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium

lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

**[00222]** Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

**[00223]** The active compounds can also be in microencapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such as magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes.

**[00224]** Dosage forms for topical or transdermal administration of a compound of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, ear drops, and eye drops are also contemplated as being within the scope of this invention. Additionally, the present invention contemplates the use of transdermal patches,

which have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms are prepared by dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

[00225] As described generally above, the compounds of the invention are useful as inhibitors of voltage-gated sodium ion channels or calcium channels, preferably N-type calcium channels. In one embodiment, the compounds and compositions of the invention are inhibitors of one or more of NaV1.1, NaV1.2, NaV1.3, NaV1.4, NaV1.5, NaV1.6, NaV1.7, NaV1.8, NaV1.9, or CaV2.2, and thus, without wishing to be bound by any particular theory, the compounds and compositions are particularly useful for treating or lessening the severity of a disease, condition, or disorder where activation or hyperactivity of one or more of NaV1.1, NaV1.2, NaV1.3, NaV1.4, NaV1.5, NaV1.6, NaV1.7, NaV1.8, NaV1.9, or CaV2.2 is implicated in the disease, condition, or disorder. When activation or hyperactivity of NaV1.1, NaV1.2, NaV1.3, NaV1.4, NaV1.5, NaV1.6, NaV1.7, NaV1.8, NaV1.9, or CaV2.2, is implicated in a particular disease, condition, or disorder, the disease, condition, or disorder may also be referred to as a "NaV1.1, NaV1.2, NaV1.3, NaV1.4, NaV1.5, NaV1.6, NaV1.7, NaV1.8 or NaV1.9-mediated disease, condition or disorder" or a "CaV2.2-mediated condition or disorder". Accordingly, in another aspect, the present invention provides a method for treating or lessening the severity of a disease, condition, or disorder where activation or hyperactivity of one or more of NaV1.1, NaV1.2, NaV1.3, NaV1.4, NaV1.5, NaV1.6, NaV1.7, NaV1.8, NaV1.9, or CaV2.2 is implicated in the disease state.

[00226] The activity of a compound utilized in this invention as an inhibitor of NaV1.1, NaV1.2, NaV1.3, NaV1.4, NaV1.5, NaV1.6, NaV1.7, NaV1.8, NaV1.9, or CaV2.2 may be assayed according to methods described generally in the Examples herein, or according to methods available to one of ordinary skill in the art.

[00227] In certain exemplary embodiments, compounds of the invention are useful as inhibitors of NaV1.8. In other embodiments, compounds of the invention are useful as inhibitors of NaV1.8 and CaV2.2. In still other embodiments, compounds of the invention are useful as inhibitors of CaV2.2.



[00228] It will also be appreciated that the compounds and pharmaceutically acceptable compositions of the present invention can be employed in combination therapies, that is, the compounds and pharmaceutically acceptable compositions can be administered concurrently with, prior to, or subsequent to, one or more other desired therapeutics or medical procedures. The particular combination of therapies (therapeutics or procedures) to employ in a combination regimen will take into account compatibility of the desired therapeutics and/or procedures and the desired therapeutic effect to be achieved. It will also be appreciated that the therapies employed may achieve a desired effect for the same disorder (for example, an inventive compound may be administered concurrently with another agent used to treat the same disorder), or they may achieve different effects (e.g., control of any adverse effects). As used herein, additional therapeutic agents that are normally administered to treat or prevent a particular disease, or condition, are known as "appropriate for the disease, or condition, being treated".

[00229] The amount of additional therapeutic agent present in the compositions of this invention will be no more than the amount that would normally be administered in a composition comprising that therapeutic agent as the only active agent. Preferably the amount of additional therapeutic agent in the presently disclosed compositions will range from about 50% to 100% of the amount normally present in a composition comprising that agent as the only therapeutically active agent.

[00230] The compounds of this invention or pharmaceutically acceptable compositions thereof may also be incorporated into compositions for coating an implantable medical device, such as prostheses, artificial valves, vascular grafts, stents and catheters. Accordingly, the present invention, in another aspect, includes a composition for coating an implantable device comprising a compound of the present invention as described generally above, and in classes and subclasses herein, and a carrier suitable for coating said implantable device. In still another aspect, the present invention includes an implantable device coated with a composition comprising a compound of the present invention as described generally above, and in classes and subclasses herein, and a carrier suitable for coating said implantable device. Suitable coatings and the general preparation of coated implantable devices are described in US Patents 6,099,562; 5,886,026; and 5,304,121. The coatings are typically biocompatible polymeric materials such as a hydrogel polymer, polymethylsiloxane, polycaprolactone, polyethylene glycol, polylactic acid, ethylene vinyl acetate, and mixtures thereof. The coatings may optionally be further

covered by a suitable topcoat of fluorosilicone, polysaccharides, polyethylene glycol, phospholipids or combinations thereof to impart controlled release characteristics in the composition.

[00231] Another aspect of the invention relates to inhibiting NaV1.1, NaV1.2, NaV1.3, NaV1.4, NaV1.5, NaV1.6, NaV1.7, NaV1.8, NaV1.9, or CaV2.2 activity in a biological sample or a patient, which method comprises administering to the patient, or contacting said biological sample with a compound of the present invention or a composition comprising said compound. The term "biological sample", as used herein, includes, without limitation, cell cultures or extracts thereof; biopsied material obtained from a mammal or extracts thereof; and blood, saliva, urine, feces, semen, tears, or other body fluids or extracts thereof.

[00232] Inhibition of NaV1.1, NaV1.2, NaV1.3, NaV1.4, NaV1.5, NaV1.6, NaV1.7, NaV1.8, NaV1.9, or CaV2.2 activity in a biological sample is useful for a variety of purposes that are known to one of skill in the art. Examples of such purposes include, but are not limited to, the study of sodium ion channels in biological and pathological phenomena; and the comparative evaluation of new sodium ion channel inhibitors.

[00233] In order that the invention described herein may be more fully understood, the following examples are set forth. It should be understood that these examples are for illustrative purposes only and are not to be construed as limiting this invention in any manner.

### EXAMPLES

#### [00234] SYNTHESIS OF EXEMPLARY COMPOUNDS OF THE INVENTION

##### [00235] Methods:

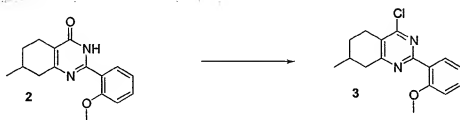
[00236] (A) Micromass MUX LCT 4 channel LC/MS, Waters 60F pump, Gilson 215 4 probe autosampler, Gilson 849 injection module, 1.5 mL/min/column flow rate, 10-99% CH<sub>3</sub>CN (0.035 % TFA) / H<sub>2</sub>O (0.05 % TFA) gradient, Phenomenex Luna 5u C18 columns (50 x 4.60 mm), Waters MUX UV-2488 UV detector, Cedex 75 ELSD detectors.

[00237] (B) PEsSciex API-150-EX LC/MS, Shimadzu LC-8A pumps, Gilson 215 autosampler, Gilson 819 injection module, 3.0 mL/min flow rate, 10-99% CH<sub>3</sub>CN (0.035 % TFA) / H<sub>2</sub>O (0.05 % TFA) gradient, Phenomenex Luna 5u C18 column (50 x 4.60 mm), Shimadzu SPD-10A UV/Vis detector, Cedex 75 ELSD detector.

[00238] (C)PESciex API-150-EX LC/MS, Shimadzu LC-8A pumps, Gilson 215 autosampler, Gilson 819 injection module, 3.0 mL/min flow rate, 40-99% CH<sub>3</sub>CN (0.035 % TFA) / H<sub>2</sub>O (0.05 % TFA) gradient, Phenomenex Luna 5u C18 column (50 x 4.60 mm), Shimadzu SPD-10A UV/Vis detector, Cedex 75 ELSD detector.



[00239] To a solution of ethyl 4-methyl-2-cyclohexanone-1-carboxylate 1 (4.7 g, 26.4 mmol) and 2-methoxy-benzamidine (5.7 g, 26.4 mmol) in ethanol (100 mL) was added NaOEt (21% in EtOH, 39.4 mL, 105.6 mmol) at 0°C. The reaction mixture was allowed to warm to room temperature and was then heated to 90°C for 12 hours. After cooling to room temperature, the solvent was removed, and the residue was taken up in ice water, extracted with DCM (50 mL x 2), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated to give a crude yellow solid. The crude mixture was purified by silica gel chromatography (65% EtOAc/35% hexane) to afford 2 (2.7 g, 9.9 mmol, 38 % yield) as a white solid. LC/MS (Method C: 10-99% CH<sub>3</sub>CN / H<sub>2</sub>O) M+1 (obs) = 272.0 retention time 2.77 min.



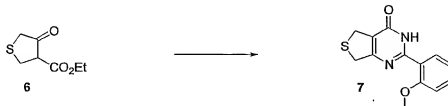
[00240] 2-(2-Methoxy-phenyl)-7-methyl-5,6,7,8-tetrahydro-3H-quinazolin-4-one 2 (2.2 g, 8.15 mmol) was dissolved in phosphorus oxychloride (50 mL) and heated to 90°C for 3 hours. The solution was cooled to room temperature and solvent removed in *vacuo*. The residue was taken up in ice water, neutralized with sat aqueous NaHCO<sub>3</sub>, extracted with dichloromethane (150 mL) (PH = 10), and concentrated to afford 3 (2.2 g, 7.61 mmol, 93% yield) as light yellow solid. LC/MS (Method C: 10-99% CH<sub>3</sub>CN / H<sub>2</sub>O) M+1 (obs) = 290.0 retention time 3.73 min.



[00241] To a solution of 4-chloroquinazoline **3** (2.2 g, 7.86 mmol) in dichloromethane (100 mL) in a round-bottomed flask equipped with rubber septum, stirring bar and nitrogen balloon was added boron tribromide (1M in DCM, 39.3 mmol) dropwise at  $-78^{\circ}\text{C}$ . The reaction was warmed to room temperature and allowed to stir for 3 hours at room temperature. Then the reaction mixture was cooled to  $-78^{\circ}\text{C}$  and quenched with saturated aqueous  $\text{NaHCO}_3$  (50 mL). After stirring for 1 hour at room temperature, the mixture was extracted with dichloromethane (2 x 100 mL), dried over  $\text{Na}_2\text{SO}_4$  and concentrated to afford **4** (2.1 g, 7.76 mmol, 97 % yield) as a light pink solid. LC/MS, (Method C: 10-99%  $\text{CH}_3\text{CN}$  /  $\text{H}_2\text{O}$ )  $\text{M}+1$  (obs) = 275.0 retention time 4.60 min.

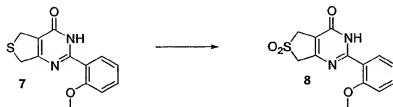


[00242] To a solution of 2-(4-chloro-7-methyl-5,6,7,8-tetrahydroquinazolin-2-yl)-phenol **4** (50 mg, 0.18 mmol) in THF (2 mL) was added triethylamine (0.072 mL, 0.54 mmol) and dimethylamine (1M in THF, 0.9 mL, 0.9 mmol). After stirring at room temperature overnight, the solvent was removed *in vacuo*. The crude mixture was purified by using Gilson HPLC to afford the TFA salt of **I-2** (47 mg, 0.12 mmol, 67% yield) as a white solid. LC/MS (Method C: 10-99%  $\text{CH}_3\text{CN}$  /  $\text{H}_2\text{O}$ )  $\text{M}+1$  (obs) = 284.0 retention time 3.17 min.

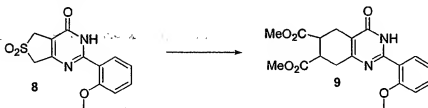


[00243] A solution of ethyl 4-oxo-tetrahydrothiophene-3-carboxylic acid ethyl ester **6** (1.0 g, 26.4 mmol) and 2-methoxy-benzamidine (5.7 g, 26.4 mmol) in ethanol (100 mL) was stirred at ambient temperature overnight, then heated at reflux for 4 hours. After cooling to

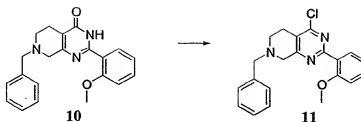
ambient temperature, the solvent was removed *in vacuo*. The crude mixture was purified by flash chromatography on silica (65% EtOAc/ 35% hexane) to afford **7** (2.7 g, 10.4 mmol, 39% yield) as a white solid. LC/MS (Method C: 10-99% CH<sub>3</sub>CN / H<sub>2</sub>O) M+1 (obs) = 261.0, retention time 2.89 min.



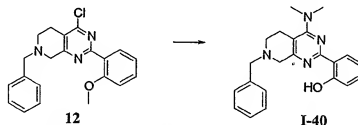
**[00244]** To a solution of 2-(2-methoxy-phenyl)-5,7-dihydro-3H-thieno[3,4-d]pyrimidine-4-one **7** (1.0 g, 3.94 mmol) in dichloromethane (100 mL) was added MCPBA (1.8 g, 7.9 mmol) in portions at ambient temperature. After stirring for 3 hours at ambient temperature, the reaction was quenched with saturated aqueous sodium thiosulfate, washed with aqueous sodium bicarbonate, water, and then extracted twice with 50 mL portions of dichloromethane. The combined organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo* to give the crude product as a yellow solid. Purification by flash chromatography on silica gel (65% EtOAc/35% hexane) gave **8** (1.1 g, 3.8 mmol, 97% yield) as a white solid. LC/MS (Method C: 10-99% CH<sub>3</sub>CN / H<sub>2</sub>O) M+1 (obs) = 293.0, retention time 2.39 min.



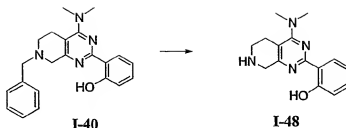
**[00245]** A solution of 2-(2-methoxy-phenyl)-6,6-dioxo-3,5,6,7-tetrahydro-6-thieno[3,4-d]pyrimidin-4-one **8** (1.0 g, 3.4 mmol) and diethyl maleate (4.3 mL, 34 mmol) in toluene (100 mL), was refluxed for 18 hours in a 150 mL round-bottomed flask equipped with a Dean-Stark trap. The solvent was removed *in vacuo* and the crude mixture purified by flash chromatography on silica gel to afford **9** (1.0 g, 2.7 mmol, 79% yield) as a white solid. LC/MS (Method C: 10-99% CH<sub>3</sub>CN / H<sub>2</sub>O) M+1 (obs) = 372.8, retention time 2.70 min.



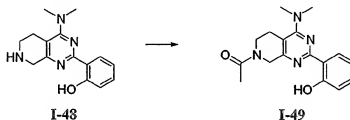
[00246] A 250 mL roundbottom flask, equipped with a reflux condenser, was charged with a mixture of **11** (2.0 g, 5.8 mmol), *N,N*-dimethylaniline (0.70 g, 5.8 mmol), and phosphoryl chloride (8.9g, 57.7 mmol). The mixture was heated, with stirring, at 95 °C for 10 minutes. The clear solution was concentrated under reduced pressure and the residue was poured onto ice (250 g) followed by the addition of CH<sub>2</sub>Cl<sub>2</sub> (500 mL). The mixture was made strongly basic by the dropwise addition of 50% aqueous NaOH solution. The organic portion was dried (MgSO<sub>4</sub>) and evaporated under reduced pressure. The residue was purified by silica gel chromatography using (70% hexanes, 30% ethyl acetate) to obtain **11** (1.6 g, 4.3 mmol, 75% yield) as a light yellow oil. LC/MS (Method C: 10-99% CH<sub>3</sub>CN / H<sub>2</sub>O) M+1 (obs) = 375.3; R<sub>t</sub> = 1.90.



[00247] A 250 mL roundbottom flask was charged with a solution of **12** (3.5 g, 9.6 mmol), and CH<sub>2</sub>Cl<sub>2</sub> (120 mL). To this solution was added boron tribromide (28.8 mL, 28.8 mmol, 1.0M in CH<sub>2</sub>Cl<sub>2</sub>) dropwise over a period of 5 minutes. The solution was stirred at 25 °C for 30 minutes. The mixture was poured into saturated aqueous NaHCO<sub>3</sub> solution (500 mL) followed by the addition of CH<sub>2</sub>Cl<sub>2</sub> (300 mL). The organic portion was dried (MgSO<sub>4</sub>) and treated with triethylamine (1.4 mL, 10.0 mmol) followed by the addition of dimethylamine (14.4 mL, 28.8 mmol, 2.0 M in THF). The mixture was stirred at ambient temperature for 1 hour. The mixture was evaporated to dryness under reduced pressure. The residue was purified by silica gel chromatography using (70% hexanes, 30% ethyl acetate) to obtain **I-40** (1.3 g, 3.6 mmol, 39% yield) as a white solid. LC/MS (Method C: 10-99% CH<sub>3</sub>CN / H<sub>2</sub>O) M+1 (obs) = 361.2; R<sub>t</sub> = 2.42.



[00248] A 250 mL roundbottom flask, equipped with a reflux condenser, was charged with a solution of I-40 (1.3 g, 3.6 mmol), AcOH (50 mL), and 10% palladium on carbon (200 mg), under an atmosphere of N<sub>2</sub>. A hydrogen balloon was introduced to the top of the reflux condenser via a needle pierced septa. The mixture was stirred and heated at 90 °C for 6 hours. The mixture was purged with N<sub>2</sub>, cooled, filtered, and the filtrate evaporated to dryness under reduced pressure to obtain compound I-48 (1.0 g, 3.6 mmol, 100% yield) as a white solid. LC/MS (Method C: 10-99% CH<sub>3</sub>CN / H<sub>2</sub>O) M+1 (obs) = 271.2; R<sub>t</sub> = 2.00.



[00249] A 2 mL vial was charged with a solution of 4 (25 mg, 0.09 mmol), triethylamine (19 mg, 18 mmol), and CH<sub>2</sub>Cl<sub>2</sub> (0.5 mL), under an atmosphere of N<sub>2</sub>. To this solution was added acetyl chloride (7.0 mg, 0.09 mmol). The mixture was stirred at 25 °C for 20 minutes. The mixture was purified by HPLC to obtain compound I-49 (32 mg, 0.07 mmol, 80% yield) as a trifluoroacetic acid salt. LC/MS (Method C: 10-99% CH<sub>3</sub>CN / H<sub>2</sub>O) M+1 (obs) = 313.2; R<sub>t</sub> = 2.18.

[00250] Other compounds of formula I have been prepared by methods substantially similar to those described above. The characterization data for these compounds is summarized in Table 3 below and includes HPLC, LC/MS (observed) and <sup>1</sup>H NMR data. Compound numbers correspond to the compound *numbers* listed in Table 2.

[00251] Table 3. Characterization Data for Selected Compounds of Formula I

Cmd	LC-MS M+1 (obs)	LC-MS R <sub>t</sub>
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Cmd	LC-MS M+1 (obs)	LC-MS R <sub>t</sub>
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Cmd	LC-MS M+1 (obs)	LC-MS R <sub>i</sub>
30	284.0	3.23
31	326.0	3.51
32	310.2	3.27
33	270.0	3.04
34	312.0	3.21
35	296.2	3.16
36	284.0	3.17
37	326.2	3.42
38	310.4	3.28
39	312.0	2.59
40	314.0	1.98
41	314.0	2.01
42	341.4	1.73
43	327.2	1.70
44	372.2	2.43
45	325.2	1.96
46	367.0	2.19
47	350.0	2.84
48	350.2	1.64
49	324.0	2.87
50	339.0	2.01
51	338.0	3.10
52	338.0	3.07
53	353.2	1.76
54	338.0	2.50
55	340.0	2.19
56	286.0	2.18
57	312.0	2.39
58	328.0	2.10
59	341.2	1.55
60	359.8	2.93
61	423.0	2.69
62	276.0	5.53
63	258.0	5.57
64	375.3	1.90
65	375.4	1.81
66	255.8	2.39
67	281.8	2.53
68	297.8	2.52
69	297.2	2.83
70	361.2	2.42
71	361.4	2.23
72	271.2	2.00
73	271.2	1.72
74	349.3	2.61
75	363.2	2.76
76	313.2	2.18
77	327.3	2.37
78	349.1	2.52
79	363.2	2.30
80	313.2	1.93

Cmd	LC-MS M+1 (obs)	LC-MS R <sub>i</sub>
81	327.2	2.41
82	285.2	2.04
83	299.2	2.43
84	290.0	2.49
85	274.0	2.75
86	405.4	2.30
87	419.2	2.52
88	391.2	2.52
89	445.2	2.84
90	429.4	2.79
91	375.2	2.86
92	428.2	3.43
93	412.4	3.06
94	386.0	2.91
95	342.0	2.89
96	383.8	2.79
97	406.4	1.93
98	368.2	2.16
99	254.8	2.20
100	281.0	2.43
101	297.0	2.15
102	295.0	2.57
103	312.8	2.41
104	309.0	2.76
105	255.0	1.88
106	281.0	2.10
107	297.2	2.12
108	295.2	2.41
109	313.0	2.44
110	325.2	2.17
111	309.4	2.63
112	300.4	2.08
113	298.3	2.07
114	243.0	2.47
115	410.0	2.76
116	397.2	2.32
117	324.0	2.93
118	324.0	2.93
119	338.0	3.51
120	326.0	3.02
121	283.9	2.68
122	353.9	2.91
123	309.9	2.73
124	397.1	3.07
125	378.1	3.16
126	283.8	2.65
127	310.0	2.79
128	323.9	3.22
129	326.1	2.97
130	337.9	3.41
131	339.1	2.64



Cmd	LC-MS M+1 (obs)	LC-MS R <sub>t</sub>
132	397.1	3.26
133	445.0	3.68
134	378.2	3.20
135	338.5	3.31
136	352.0	3.31
137	366.2	3.52
138	425.2	3.39

Cmd	LC-MS M+1 (obs)	LC-MS R <sub>t</sub>
139	417.1	3.11
140	403.1	2.99
141	431.1	3.23
142	345.9	3.11
143	359.9	3.46
144	339.9	2.91
145	356.1	3.04

**[00252] ASSAYS FOR DETECTING AND MEASURING NaV INHIBITION PROPERTIES OF COMPOUNDS**

**[00253]** A) Optical methods for assaying NaV inhibition properties of compounds:

**[00254]** Compounds of the invention are useful as antagonists of voltage-gated sodium ion channels. Antagonist properties of test compounds were assessed as follows. Cells expressing the NaV of interest were placed into microtiter plates. After an incubation period, the cells were stained with fluorescent dyes sensitive to the transmembrane potential. The test compounds were added to the microtiter plate. The cells were stimulated with either a chemical or electrical means to evoke a NaV dependent membrane potential change from unblocked channels, which was detected and measured with trans-membrane potential-sensitive dyes. Antagonists were detected as a decreased membrane potential response to the stimulus. The optical membrane potential assay utilized voltage-sensitive FRET sensors described by Gonzalez and Tsien (See, Gonzalez, J. E. and R. Y. Tsien (1995) "Voltage sensing by fluorescence resonance energy transfer in single cells" Biophys J 69(4): 1272-80, and Gonzalez, J. E. and R. Y. Tsien (1997) "Improved indicators of cell membrane potential that use fluorescence resonance energy transfer" Chem Biol 4(4): 269-77) in combination with instrumentation for measuring fluorescence changes such as the Voltage/Ion Probe Reader (VIPR<sup>®</sup>) (See, Gonzalez, J. E., K. Oades, et al. (1999) "Cell-based assays and instrumentation for screening ion-channel targets" Drug Discov Today 4(9): 431-439).

**[00255]** B) VIPR<sup>®</sup> optical membrane potential assay method with chemical stimulation

**[00256]** Cell Handling and Dye Loading

**[00257]** 24 hours before the assay on VIPR, CHO cells endogenously expressing a NaV1.2 type voltage-gated NaV are seeded in 96-well poly-lysine coated plates at 60,000 cells per well. Other subtypes are performed in an analogous mode in a cell line expressing the NaV of interest.

- 1) On the day of the assay, medium is aspirated and cells are washed twice with 225  $\mu$ L of Bath Solution #2 (BS#2).
- 2) A 15  $\mu$ M CC2-DMPE solution is prepared by mixing 5 mM coumarin stock solution with 10% Pluronic 127 1:1 and then dissolving the mix in the appropriate volume of BS#2.
- 3) After bath solution is removed from the 96-well plates, the cells are loaded with 80  $\mu$ L of the CC2-DMPE solution. Plates are incubated in the dark for 30 minutes at room temperature.
- 4) While the cells are being stained with coumarin, a 15  $\mu$ L oxonol solution in BS#2 is prepared. In addition to DiSBAC<sub>2</sub>(3), this solution should contain 0.75 mM ABSC1 and 30  $\mu$ L veratridine (prepared from 10 mM EtOH stock, Sigma #V-5754).
- 5) After 30 minutes, CC2-DMPE is removed and the cells are washed twice with 225  $\mu$ L of BS#2. As before, the residual volume should be 40  $\mu$ L.
- 6) Upon removing the bath, the cells are loaded with 80  $\mu$ L of the DiSBAC<sub>2</sub>(3) solution, after which test compound, dissolved in DMSO, is added to achieve the desired test concentration to each well from the drug addition plate and mixed thoroughly. The volume in the well should be roughly 121  $\mu$ L. The cells are then incubated for 20-30 minutes.
- 7) Once the incubation is complete, the cells are ready to be assayed on VIPR<sup>®</sup> with a sodium addback protocol. 120  $\mu$ L of Bath solution #1 is added to stimulate the NaV dependent depolarization. 200  $\mu$ L tetracaine was used as an antagonist positive control for block of the NaV channel.

**[00258]** Analysis of VIPR<sup>®</sup> Data:

**[00259]** Data are analyzed and reported as normalized ratios of background-subtracted emission intensities measured in the 460 nm and 580 nm channels. Background intensities are then subtracted from each assay channel. Background intensities are obtained by measuring the emission intensities during the same time periods from identically treated assay wells in which there are no cells. The response as a function of time is then reported as the ratios obtained using the following formula:

$$R(t) = \frac{(\text{intensity}_{460 \text{ nm}} - \text{background}_{460 \text{ nm}})}{(\text{intensity}_{580 \text{ nm}} - \text{background}_{580 \text{ nm}})}$$

[00260] The data is further reduced by calculating the initial ( $R_i$ ) and final ( $R_f$ ) ratios. These are the average ratio values during part or all of the pre-stimulation period, and during sample points during the stimulation period. The response to the stimulus  $R = R_f/R_i$  is then calculated. For the  $\text{Na}^+$  addback analysis time windows, baseline is 2-7 sec and final response is sampled at 15-24 sec.

[00261] Control responses are obtained by performing assays in the presence of a compound with the desired properties (positive control), such as tetracaine, and in the absence of pharmacological agents (negative control). Responses to the negative ( $N$ ) and positive ( $P$ ) controls are calculated as above. The compound antagonist activity  $A$  is defined as:

$$A = \frac{R - P}{N - P} * 100 \quad \text{where } R \text{ is the ratio response of the test compound}$$

#### Solutions [mM]

Bath Solution #1: NaCl 160, KCl 4.5,  $\text{CaCl}_2$  2,  $\text{MgCl}_2$  1, HEPES 10, pH 7.4 with NaOH

Bath Solution #2 TMA-Cl 160,  $\text{CaCl}_2$  0.1,  $\text{MgCl}_2$  1, HEPES 10, pH 7.4 with KOH (final K concentration ~ 5 mM)

CC2-DMPE: prepared as a 5 mM stock solution in DMSO and stored at  $-20^\circ\text{C}$

DiSBAC<sub>2</sub>(3): prepared as a 12 mM stock in DMSO and stored at  $-20^\circ\text{C}$

ABSC1: prepared as a 200 mM stock in distilled  $\text{H}_2\text{O}$  and stored at room temperature

#### [00262] Cell Culture

[00263] CHO cells are grown in DMEM (Dulbecco's Modified Eagle Medium; GibcoBRL #10569-010) supplemented with 10% FBS (Fetal Bovine Serum, qualified; GibcoBRL #16140-

071) and 1% Pen-Strep (Penicillin-Streptomycin; GibcoBRL #15140-122). Cells are grown in vented cap flasks, in 90% humidity and 10% CO<sub>2</sub>, to 100% confluence. They are usually split by trypsinization 1:10 or 1:20, depending on scheduling needs, and grown for 2-3 days before the next split.

**[00264] C) VIPR<sup>®</sup> optical membrane potential assay method with electrical stimulation**

**[00265]** The following is an example of how NaV1.3 inhibition activity is measured using the optical membrane potential method#2. Other subtypes are performed in an analogous mode in a cell line expressing the NaV of interest.

**[00266]** HEK293 cells stably expressing NaV1.3 are plated into 96-well microtiter plates. After an appropriate incubation period, the cells are stained with the voltage sensitive dyes CC2-DMPE/DiSBAC<sub>2</sub>(3) as follows.

**[00267] Reagents:**

100 mg/mL Pluronic F-127 (Sigma #P2443), in dry DMSO

10 mM DiSBAC<sub>2</sub>(3) (Aurora #00-100-010) in dry DMSO

10 mM CC2-DMPE (Aurora #00-100-008) in dry DMSO

200 mM ABSC1 in H<sub>2</sub>O

Hank's Balanced Salt Solution (Hyclone #SH30268.02) supplemented with 10 mM HEPES (Gibco #15630-080)

**[00268] Loading protocol:**

**[00269] 2X CC2-DMPE = 20  $\mu$ M CC2-DMPE:** 10 mM CC2-DMPE is vortexed with an equivalent volume of 10% pluronic, followed by vortexing in required amount of HBSS containing 10 mM HEPES. Each cell plate will require 5 mL of 2X CC2-DMPE. 50  $\mu$ L of 2X CC2-DMPE is to wells containing washed cells, resulting in a 10  $\mu$ M final staining concentration. The cells are stained for 30 minutes in the dark at RT.

**[00270] 2X DiSBAC<sub>2</sub>(3) with ABSC1 = 6 $\mu$ M DiSBAC<sub>2</sub>(3) and 1 mM ABSC1:** The required amount of 10 mM DiSBAC<sub>2</sub>(3) is added to a 50 ml conical tube and mixed with 1  $\mu$ L 10% pluronic for each mL of solution to be made and vortexed together. Then HBSS/HEPES is added to make up 2X solution. Finally, the ABSC1 is added.

[00271] The 2X DiSBAC<sub>2</sub>(3) solution can be used to solvate compound plates. Note that compound plates are made at 2X drug concentration. Wash stained plate again, leaving residual volume of 50  $\mu$ L. Add 50  $\mu$ L/well of the 2X DiSBAC<sub>2</sub>(3) w/ ABSC1. Stain for 30 minutes in the dark at RT.

[00272] The electrical stimulation instrument and methods of use are described in ION Channel Assay Methods PCT/US01/21652, herein incorporated by reference. The instrument comprises a microtiter plate handler, an optical system for exciting the coumarin dye while simultaneously recording the coumarin and oxonol emissions, a waveform generator, a current-voltage-controlled amplifier, and a device for inserting electrodes in well. Under integrated computer control, this instrument passes user-programmed electrical stimulus protocols to cells within the wells of the microtiter plate.

[00273] Reagents

[00274] Assay buffer #1

140 mM NaCl, 4.5 mM KCl, 2 mM CaCl<sub>2</sub>, 1 mM MgCl<sub>2</sub>, 10 mM HEPES, 10 mM glucose, pH 7.40, 330 mOsm

Pluronic stock (1000X): 100 mg/mL pluronic 127 in dry DMSO

Oxonol stock (3333X): 10 mM DiSBAC<sub>2</sub>(3) in dry DMSO

Coumarin stock (1000X): 10 mM CC2-DMPE in dry DMSO

ABSC1 stock (400X): 200 mM ABSC1 in water

[00275] Assay Protocol

1. Insert or use electrodes into each well to be assayed.
2. Use the current-controlled amplifier to deliver stimulation wave pulses for 3 s. Two seconds of pre-stimulus recording are performed to obtain the un-stimulated intensities. Five seconds of post-stimulation recording are performed to examine the relaxation to the resting state.

[00276] Data Analysis

[00277] Data are analyzed and reported as normalized ratios of background-subtracted emission intensities measured in the 460 nm and 580 nm channels. Background intensities are

then subtracted from each assay channel. Background intensities are obtained by measuring the emission intensities during the same time periods from identically treated assay wells in which there are no cells. The response as a function of time is then reported as the ratios obtained using the following formula:

$$R(t) = \frac{(\text{intensity}_{460\text{ nm}} - \text{background}_{460\text{ nm}})}{(\text{intensity}_{580\text{ nm}} - \text{background}_{580\text{ nm}})}$$

**[00278]** The data is further reduced by calculating the initial ( $R_i$ ) and final ( $R_f$ ) ratios. These are the average ratio values during part or all of the pre-stimulation period, and during sample points during the stimulation period. The response to the stimulus  $R = R_f/R_i$  is then calculated.

**[00279]** Control responses are obtained by performing assays in the presence of a compound with the desired properties (positive control), such as tetracaine, and in the absence of pharmacological agents (negative control). Responses to the negative ( $N$ ) and positive ( $P$ ) controls are calculated as above. The compound antagonist activity  $A$  is defined as:

$$A = \frac{R - P}{N - P} * 100 \quad \text{where } R \text{ is the ratio response of the test compound.}$$

#### **[00280]** ELECTROPHYSIOLOGY ASSAYS FOR NaV ACTIVITY AND INHIBITION OF TEST COMPOUNDS

**[00281]** Patch clamp electrophysiology was used to assess the efficacy and selectivity of sodium channel blockers in dorsal root ganglion neurons. Rat neurons were isolated from the dorsal root ganglions and maintained in culture for 2 to 10 days in the presence of NGF (50 ng/ml) (culture media consisted of NeurobasalA supplemented with B27, glutamine and antibiotics). Small diameter neurons (nociceptors, 8-12  $\mu\text{m}$  in diameter) have been visually identified and probed with fine tip glass electrodes connected to an amplifier (Axon Instruments). The "voltage clamp" mode has been used to assess the compound's IC50 holding the cells at -60 mV. In addition, the "current clamp" mode has been employed to test the efficacy of the compounds in blocking action potential generation in response to current

injections. The results of these experiments have contributed to the definition of the efficacy profile of the compounds.

**[00282]** VOLTAGE-CLAMP assay in DRG neurons

**[00283]** TTX-resistant sodium currents were recorded from DRG somata using the whole-cell variation of the patch clamp technique. Recordings were made at room temperature ( $\sim 22^{\circ}\text{C}$ ) with thick walled borosilicate glass electrodes (WPI; resistance 3-4 M $\Omega$ ) using an Axopatch 200B amplifier (Axon Instruments). After establishing the whole-cell configuration, approximately 15 minutes were allowed for the pipette solution to equilibrate within the cell before beginning recording. Currents were lowpass filtered between 2-5 kHz and digitally sampled at 10 kHz. Series resistance was compensated 60-70% and was monitored continuously throughout the experiment. The liquid junction potential ( $\sim 7\text{ mV}$ ) between the intracellular pipette solution and the external recording solution was not accounted for in the data analysis. Test solutions were applied to the cells with a gravity driven fast perfusion system (SF-77; Warner Instruments).

**[00284]** Dose-response relationships were determined in voltage clamp mode by repeatedly depolarizing the cell from the experiment specific holding potential to a test potential of +10mV once every 60 seconds. Blocking effects were allowed to plateau before proceeding to the next test concentration.

**[00285]** Solutions

**[00286]** Intracellular solution (in mM): Cs-F (130), NaCl (10), MgCl<sub>2</sub> (1), EGTA (1.5), CaCl<sub>2</sub> (0.1), HEPES (10), glucose (2), pH = 7.42, 290 mOsm.

**[00287]** Extracellular solution (in mM): NaCl (138), CaCl<sub>2</sub> (1.26), KCl (5.33), KH<sub>2</sub>PO<sub>4</sub> (0.44), MgCl<sub>2</sub> (0.5), MgSO<sub>4</sub> (0.41), NaHCO<sub>3</sub> (4), Na<sub>2</sub>HPO<sub>4</sub> (0.3), glucose (5.6), HEPES (10), CdCl<sub>2</sub> (0.4), NiCl<sub>2</sub> (0.1), TTX ( $0.25 \times 10^{-3}$ ).

**[00288]** CURRENT-CLAMP assay for NaV channel inhibition activity of compounds

**[00289]** Cells were current-clamped in whole-cell configuration with a Multiamp 700A amplifier (Axon Inst). Borosilicate pipettes (4-5 M $\Omega$ ) were filled with (in mM): 150 K-glucuronate, 10 NaCl, 0.1 EGTA, 10 Hepes, 2 MgCl<sub>2</sub>, (buffered to pH 7.34 with KOH). Cells were bathed in (in mM): 140 NaCl, 3 KCl, 1 MgCl, 1 CaCl, and 10 Hepes). Pipette potential was

zeroed before seal formation; liquid junction potentials were not corrected during acquisition. Recordings were made at room temperature.

[00290] Compounds of the invention as depicted generally herein and in Table 2 were found to inhibit voltage-gated sodium channels at 25.0  $\mu\text{M}$  or less.

**[00291] ASSAYS FOR DETECTING AND MEASURING CaV INHIBITION**  
**PROPERTIES OF COMPOUNDS**

[00292] A) Optical methods for assaying CaV inhibition properties of compounds:

[00293] Compounds of the invention are useful as antagonists of voltage-gated calcium ion channels. Antagonist properties of test compounds were assessed as follows. Cells expressing the CaV of interest were placed into microtiter plates. After an incubation period, the cells were stained with fluorescent dyes sensitive to the transmembrane potential. The test compounds were added to the microtiter plate. The cells were stimulated with electrical means to evoke a CaV dependent membrane potential change from unblocked channels, which was detected and measured with trans-membrane potential-sensitive dyes. Antagonists were detected as a decreased membrane potential response to the stimulus. The optical membrane potential assay utilized voltage-sensitive FRET sensors described by Gonzalez and Tsien (See, Gonzalez, J. E. and R. Y. Tsien (1995) "Voltage sensing by fluorescence resonance energy transfer in single cells" Biophys J 69(4): 1272-80, and Gonzalez, J. E. and R. Y. Tsien (1997) "Improved indicators of cell membrane potential that use fluorescence resonance energy transfer" Chem Biol 4(4): 269-77) in combination with instrumentation for measuring fluorescence changes such as the Voltage/Ion Probe Reader (VIPR<sup>®</sup>) (See, Gonzalez, J. E., K. Oades, et al. (1999) "Cell-based assays and instrumentation for screening ion-channel targets" Drug Discov Today 4(9): 431-439).

[00294] VIPR<sup>®</sup> optical membrane potential assay method with electrical stimulation

[00295] The following is an example of how CaV2.2 inhibition activity is measured using the optical membrane potential method. Other subtypes are performed in an analogous mode in a cell line expressing the CaV of interest.

[00296] HEK293 cells stably expressing CaV2.2 are plated into 96-well microtiter plates. After an appropriate incubation period, the cells are stained with the voltage sensitive dyes CC2-DMPE/DisBAC2(3) as follows.



**Reagents:**

100 mg/mL Pluronic F-127 (Sigma #P2443), in dry DMSO

10 mM DiSBAC<sub>6</sub>(3) (Aurora #00-100-010) in dry DMSO

10 mM CC2-DMPE (Aurora #00-100-008) in dry DMSO

200 mM Acid Yellow 17 (Aurora #VABSC) in H<sub>2</sub>O

370mM Barium Chloride (Sigma Cat# B6394) in H<sub>2</sub>O

**Bath X**

160mM NaCl (Sigma Cat# S-9888)

4.5mM KCl (Sigma Cat# P-5405)

1mM MgCl<sub>2</sub> (Fluka Cat# 63064)

10mM HEPES (Sigma Cat# H-4034)

pH 7.4 using NaOH

**[00297] Loading rotocol:**

**[00298] 2X CC2-DMPE = 20  $\mu$ M CC2-DMPE:** 10 mM CC2-DMPE is vortexed with an equivalent volume of 10% pluronic, followed by vortexing in required amount of HBSS containing 10 mM HEPES. Each cell plate will require 5 mL of 2X CC2-DMPE. 50  $\mu$ L of 2X CC2-DMPE is added to wells containing washed cells, resulting in a 10  $\mu$ M final staining concentration. The cells are stained for 30 minutes in the dark at RT.

**[00299] 2X CC2DMPE & DISBAC<sub>6</sub>(3) = 8  $\mu$ M CC2DMPE & 2. 5  $\mu$ M DISBAC<sub>6</sub>(3):** Vortex together both dyes with an equivalent volume of 10% pluronic (in DMSO). Vortex in required amount of Bath X with beta-cyclodextrin. Each 96well cell plate will require 5 ml of 2XCC2DMPE. Wash plate with ELx405 with Bath X, leaving a residual volume of 50  $\mu$ L/well. Add 50  $\mu$ L of 2XCC2DMPE & DISBAC<sub>6</sub>(3) to each well. Stain for 30 minutes in the dark at RT.

**[00300] 1. 5X AY17 = 750  $\mu$ M AY17 with 15mM BaCl<sub>2</sub>:** Add Acid Yellow 17 to vessel containing Bath X. Mix well. Allow solution to sit for 10 minutes. Slowly mix in 370mM BaCl<sub>2</sub>. This solution can be used to solvate compound plates. Note that compound plates are made at 1.5X drug concentration and not the usual 2X. Wash CC2 stained plate, again, leaving

residual volume of 50  $\mu$ L. Add 100  $\mu$ L/well of the AY17 solution. Stain for 15 minutes in the dark at RT. Run plate on the optical reader.

**[00301]** The electrical stimulation instrument and methods of use are described in ION Channel Assay Methods PCT/US01/21652, herein incorporated by reference. The instrument comprises a microtiter plate handler, an optical system for exciting the coumarin dye while simultaneously recording the coumarin and oxonol emissions, a waveform generator, a current- or voltage-controlled amplifier, and a device for inserting electrodes in well. Under integrated computer control, this instrument passes user-programmed electrical stimulus protocols to cells within the wells of the microtiter plate.

**[00302]** Assay Protocol

**[00303]** Insert or use electrodes into each well to be assayed.

**[00304]** Use the current-controlled amplifier to deliver stimulation wave pulses for 3-5 s. Two seconds of pre-stimulus recording are performed to obtain the un-stimulated intensities. Five seconds of post-stimulation recording are performed to examine the relaxation to the resting state.

**[00305]** Data Analysis

**[00306]** Data are analyzed and reported as normalized ratios of background-subtracted emission intensities measured in the 460 nm and 580 nm channels. Background intensities are then subtracted from each assay channel. Background intensities are obtained by measuring the emission intensities during the same time periods from identically treated assay wells in which there are no cells. The response as a function of time is then reported as the ratios obtained using the following formula:

$$R(t) = \frac{(\text{intensity}_{460\text{ nm}} - \text{background}_{460\text{ nm}})}{(\text{intensity}_{580\text{ nm}} - \text{background}_{580\text{ nm}})}$$

**[00307]** The data is further reduced by calculating the initial ( $R_i$ ) and final ( $R_f$ ) ratios. These are the average ratio values during part or all of the pre-stimulation period, and during sample points during the stimulation period. The response to the stimulus  $R = R_f/R_i$  is then calculated.

[00308] Control responses are obtained by performing assays in the presence of a compound with the desired properties (positive control), such as mibefradil, and in the absence of pharmacological agents (negative control). Responses to the negative (*N*) and positive (*P*) controls are calculated as above. The compound antagonist activity *A* is defined as:

$$A = \frac{R - P}{N - P} * 100 \quad \text{where R is the ratio response of the test compound.}$$

[00309] ELECTROPHYSIOLOGY ASSAYS FOR CaV ACTIVITY AND INHIBITION OF TEST COMPOUNDS

[00310] Patch clamp electrophysiology was used to assess the efficacy of calcium channel blockers expressed in HEK293 cells. HEK293 cells expressing CaV2.2 have been visually identified and probed with fine tip glass electrodes connected to an amplifier (Axon Instruments). The "voltage clamp" mode has been used to assess the compound's IC50 holding the cells at -100 mV. The results of these experiments have contributed to the definition of the efficacy profile of the compounds.

[00311] VOLTAGE-CLAMP assay in HEK293 cells expressing CaV2.2

[00312] CaV2.2 calcium currents were recorded from HEK293 cells using the whole-cell variation of the patch clamp technique. Recordings were made at room temperature (~22° C) with thick walled borosilicate glass electrodes (WPI; resistance 3-4 MΩ) using an Axopatch 200B amplifier (Axon Instruments). After establishing the whole-cell configuration, approximately 15 minutes were allowed for the pipette solution to equilibrate within the cell before beginning recording. Currents were lowpass filtered between 2-5 kHz and digitally sampled at 10 kHz. Series resistance was compensated 60-70% and was monitored continuously throughout the experiment. The liquid junction potential (-7 mV) between the intracellular pipette solution and the external recording solution was not accounted for in the data analysis. Test solutions were applied to the cells with a gravity driven fast perfusion system (SF-77; Warner Instruments).

[00313] Dose-response relationships were determined in voltage clamp mode by repeatedly depolarizing the cell from the experiment specific holding potential to a test potential of +20mV for 50ms at frequencies of 0.1, 1, 5, 10, 15, and 20 Hz. Blocking effects were allowed to plateau before proceeding to the next test concentration.

[00314] Solutions

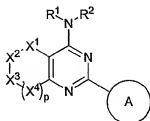
[00315] Intracellular solution (in mM): Cs-F (130), NaCl (10),  $\text{MgCl}_2$  (1), EGTA (1.5),  $\text{CaCl}_2$  (0.1), HEPES (10), glucose (2), pH = 7.42, 290 mOsm.

[00316] Extracellular solution (in mM): NaCl (138),  $\text{BaCl}_2$  (10), KCl (5.33),  $\text{KH}_2\text{PO}_4$  (0.44),  $\text{MgCl}_2$  (0.5),  $\text{MgSO}_4$  (0.41),  $\text{NaHCO}_3$  (4),  $\text{Na}_2\text{HPO}_4$  (0.3), glucose (5.6), HEPES (10).

[00317] Following these procedures, representative compounds of the present invention were found to possess desired N-type calcium channel modulation activity and selectivity.

## Claims

1. A compound of formula I:



## I

or a pharmaceutically acceptable salt thereof, wherein:

p is 0, 1 or 2;

X<sup>1</sup>, X<sup>2</sup>, X<sup>3</sup> and X<sup>4</sup> are each independently selected from NR<sup>3</sup>, C=O, CHR<sup>4</sup>, S, O, S=O, or SO<sub>2</sub>;

R<sup>1</sup> and R<sup>2</sup> are each independently hydrogen, or an optionally substituted group selected from C<sub>1-6</sub> aliphatic, a 5-6 membered aryl ring having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or R<sup>1</sup> and R<sup>2</sup>, taken together with the nitrogen atom to which they are bound, form an optionally substituted 3-8 membered heterocyclyl or heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein R<sup>1</sup>, R<sup>2</sup>, or any ring formed by R<sup>1</sup> and R<sup>2</sup> taken together, are each independently optionally substituted at one or more carbon atoms with 0-4 occurrences of -R<sup>5</sup>, and at one or more substitutable nitrogen atoms with -R<sup>6</sup>;

Ring A is a 5-6 membered monocyclic or 8-10 membered bicyclic aryl ring having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, optionally substituted at one or more carbon atoms with 0-5 occurrences of -R<sup>7</sup>, and at one or more substitutable nitrogen atoms with -R<sup>8</sup>;

each occurrence of R<sup>4</sup>, R<sup>5</sup>, and R<sup>7</sup> is independently Q-R<sup>X</sup>; wherein Q is a bond or is a C<sub>1</sub>-C<sub>6</sub> alkylidene chain wherein up to two non-adjacent methylene units of Q are optionally and



- 2) when  $X^1$ ,  $X^2$  and  $X^4$  are  $\text{CH}_2$ ; and  $X^3$  is S, then Ring A is not unsubstituted phenyl;
- iv) when  $R^1$  and  $R^2$ , taken together with the nitrogen atom, is N-piperizinyl,  $X^1$ ,  $X^2$  and  $X^3$  are  $\text{CH}_2$ , and  $X^4$  is S, then Ring A is not 3- $\text{NO}_2\text{Ph}$ , 4-pyridinyl, or unsubstituted phenyl;
- v) when one of  $X^1$ ,  $X^2$ ,  $X^3$  or  $X^4$  is  $\text{NR}^3$  and the others of  $X^1$ ,  $X^2$ ,  $X^3$  or  $X^4$  are each  $\text{CH}_2$ , and  $R^1$  and  $R^2$  are each Me, H,  $\text{CH}_2\text{Ph}$ , or  $(\text{CH}_2)_2\text{NMe}_2$ , then Ring A is not pyrid-2-yl substituted at the 6-position;
- vi) when  $X^1$ ,  $X^2$ , and  $X^3$  are each  $\text{CH}_2$ ,  $X^4$  is S,  $R^1$  is H, and  $R^2$  is  $-\text{CH}_2-\text{C}\equiv\text{CH}$ , then Ring A is not unsubstituted phenyl;
- vii) when  $X^1$  is  $\text{NMe}$ ;  $X^2$ ,  $X^3$  and  $X^4$  are each  $\text{CH}_2$ ,  $R^1$  is H, and  $R^2$  is unsubstituted phenyl, then Ring A is not unsubstituted phenyl; and
- viii) when  $X^1$ ,  $X^2$  and  $X^4$  are each  $\text{CH}_2$ ,  $X^3$  is S,  $R^1$  and  $R^2$  are each Me, then Ring A is not unsubstituted phenyl; and
- e) when p is 0, then:
- i) when  $X^1$  is  $\text{CH}_2$ ,  $X^2$  is  $\text{NR}^3$ ,  $X^3$  is  $\text{C}=\text{O}$ ; or  $X^1$  is  $\text{C}=\text{O}$ ,  $X^2$  is  $\text{CHR}^4$ , and  $X^3$  is  $\text{NR}^3$ ; or  $X^2$  is  $\text{NR}^3$ ,  $X^2$  is  $\text{C}=\text{O}$ , and  $X^3$  is  $\text{CHR}^4$ ; or  $X^1$  is  $\text{CH}_2$ ,  $X^2$  is O, and  $X^3$  is  $\text{C}=\text{O}$ , then when  $R^1$  is hydrogen and  $R^2$  is unsubstituted phenyl or  $-\text{CH}_2\text{CH}_2\text{Cl}$ , or when  $R^1$  and  $R^2$ , taken together form optionally substituted piperazinyl, morpholino, piperidinyl, or pyrrolidinyl, then Ring A is not optionally substituted piperidinyl, piperazinyl, morpholino, or pyrrolidinyl;
- ii) when  $X^1$  is  $\text{CHR}^4$ ,  $X^2$  is  $\text{SO}_2$ , and  $X^3$  is  $\text{CHR}^4$ , and  $R^1$  and  $R^2$ , taken together are piperazinyl, then Ring A is not unsubstituted phenyl;
- iii) when  $X^1$  and  $X^2$  are  $\text{CHR}^4$ ,  $X^3$  is O,  $R^1$  is hydrogen, and  $R^2$  is  $-\text{C}(=\text{O})\text{CH}_3$ , then Ring A is not substituted furyl;
- iv) when  $X^1$  is S,  $X^2$  is  $\text{CHR}^4$ ,  $X^3$  is  $\text{CHR}^4$ ; or  $X^1$  is  $\text{CHR}^4$ ,  $X^2$  is S, and  $X^3$  is  $\text{CHR}^4$ ; or  $X^1$  and  $X^2$  are  $\text{CHR}^4$  and  $X^3$  is S, then Ring A is not optionally substituted N-linked morpholino, pyrrolidinyl, piperazinyl, piperidinyl, or is not unsubstituted phenyl or cyclopropyl;
- v) when  $X^1$  is  $\text{CHR}^4$ ,  $X^2$  is  $\text{NR}^3$ ,  $X^3$  is  $\text{CHR}^4$ , and  $R^1$  and  $R^2$  are both methyl, then Ring A is not 6-methyl-2-pyridyl;

vi) when  $X^1$  is  $NR^3$ ,  $X^2$  is  $C=O$ ,  $X^3$  is  $NR^3$ , and  $R^1$  and  $R^2$  are both methyl, then Ring A is not unsubstituted phenyl; and

vii) when  $X^1$  and  $X^2$  are  $CHR^4$ ,  $X^3$  is  $NR^3$ ,  $R^1$  is hydrogen, and  $R^2$  is unsubstituted phenyl, then Ring A is not unsubstituted phenyl; and

further provided that:

- a) when each of  $X^1$ ,  $X^2$ ,  $X^3$ , and  $X^4$  is  $CHR^4$  and p is 0 or 1, then at least one  $R^4$  is other than hydrogen;
- b) when each of  $X^1$ ,  $X^2$ ,  $X^3$ , and  $X^4$  is  $CHR^4$  and Ring A is a substituted or unsubstituted piperizinyl group, then at least one  $R^4$  is other than hydrogen;
- c) when each of  $X^1$ ,  $X^2$ ,  $X^3$ , and  $X^4$  is  $CHR^4$ ,  $R^1$  is hydrogen, and  $R^2$  is 1H-indazol-3-yl, 7-fluoro-1H-indazol-3-yl, 5-fluoro-1H-indazol-3-yl, 5,7-difluoro-1H-indazol-3-yl or 5-methyl-1H-pyrazolyl, and Ring A is an unsubstituted phenyl group or is a phenyl group substituted in the ortho position with Cl or  $CF_3$ , then at least one  $R^4$  is other than hydrogen; and
- d) 5(6H)-quinazolinone, 4-anilino-7,8-dihydro-2,7-diphenyl- and 5(6H)-quinazolinone, 4-anilino-7,8-dihydro-7,7-dimethyl-2-phenyl- are excluded.

2. The compound according to claim 1, wherein p is 0 or 1.

3. The compound according to claim 1, wherein Ring A is a 5-6 membered aryl ring having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, optionally substituted at one or more carbon atoms with 0-5 occurrences of  $-R^7$ , and at one or more substitutable nitrogen atoms with  $-R^8$ , wherein  $R^7$  and  $R^8$  are as defined above.

4. The compound according to claim 1, wherein:

$X^1$ ,  $X^2$ , and  $X^4$  are  $CH_2$ , and  $X^3$  is  $CH-Me$  or  $N-(C_{1-4} \text{ alkyl})$ , N-benzyl;

p is 0, 1 or 2;

$R^1$  is methyl and  $R^2$  is furan-2-ylmethyl, dimethylaminoethyl, or methyl; or



$R^1$  and  $R^2$  taken together form piperidinyl, piperazinyl, 4-methylpiperidinyl, 4- $C_{1-4}$  alkoxy piperidinyl, morpholinyl, 4-carboxy- $C_{1-4}$ alkylpiperazinyl, or 4- $C_{1-4}$  alkylsulfonylpiperazinyl; and

ring A is 2-hydroxyphenyl, 2-hydroxy-6-fluorophenyl, phenyl-2-disodium phosphate, or pyrrolyl.

5. The compound according to claim 4, wherein:

$X^1$ ,  $X^2$ , and  $X^4$  are  $CH_2$ , and  $X^3$  is CH-Me or N-Me;

p is 1;

$R^1$  is methyl and  $R^2$  is furan-2-ylmethyl or methyl; or

$R^1$  and  $R^2$  taken together form piperidinyl, 4-methylpiperidinyl, morpholinyl, or 4- $C_{1-4}$  alkylsulfonylpiperazinyl; and

ring A is 2-hydroxyphenyl or 2-hydroxy-6-fluorophenyl.

6. The compound according to claim 5, wherein:

$X^1$ ,  $X^2$ , and  $X^4$  are  $CH_2$ , and  $X^3$  is CH-Me;

p is 1;

$R^1$  is methyl and  $R^2$  is furan-2-ylmethyl or methyl; or

$R^1$  and  $R^2$  taken together form piperidinyl, 4-methylpiperidinyl, or 4- $C_{1-4}$  alkylsulfonylpiperazinyl; and

ring A is 2-hydroxyphenyl or 2-hydroxy-6-fluorophenyl.

7. The compound according to claim 6, wherein:

$X^1$ ,  $X^2$ , and  $X^4$  are  $CH_2$ , and  $X^3$  is CH-Me;

p is 1;

$R^1$  and  $R^2$  taken together form 4-methylpiperidinyl or 4- $C_{1-4}$  alkylsulfonylpiperazinyl;

and

ring A is 2-hydroxy or 2-hydroxy-6-fluorophenyl.

8. The compound according to claim 1, wherein:

$X^1$ , and  $X^2$  are  $CH_2$ ,  $X^4$  is CHOH or  $CH_2$ , and  $X^3$  is  $CH_2$ , CH-Me, or C(O)-Me;

p is 1;

R<sup>1</sup> is methyl and R<sup>2</sup> methyl or methylaminoethyl; or

R<sup>1</sup> and R<sup>2</sup> taken together form 1-piperidinyl, 1-piperazinyl, or 4-methylpiperazinyl; and  
ring A is 2-hydroxyphenyl, 2-fluorophenyl, or 1-pyrrolyl.

9. The compound according to claim 8, wherein:

X<sup>1</sup>, X<sup>2</sup>, and X<sup>4</sup> are CH<sub>2</sub>, and X<sup>3</sup> is CH<sub>2</sub> or CH-Me;

p is 1;

R<sup>1</sup> is methyl and R<sup>2</sup> is methyl or methylaminoethyl; or

R<sup>1</sup> and R<sup>2</sup> taken together form 1-piperazinyl or 4-methylpiperazinyl; and  
ring A is 2-hydroxyphenyl or 1-pyrrolyl.

10. The compound according to claim 1, wherein:

X<sup>1</sup> and X<sup>4</sup> are CH<sub>2</sub>, X<sup>2</sup> is CH<sub>2</sub>, CHMe, or C(O)OMe, and X<sup>3</sup> is N-benzyl, N-(3-methoxybenzyl), N-(4-carboxymethylbenzyl), CH<sub>2</sub>, or CH-Me;

p is 1;

R<sup>1</sup> is methyl or benzyl and R<sup>2</sup> is methyl or dimethylaminoethyl; or

R<sup>1</sup> and R<sup>2</sup> taken together form a 1-piperazinyl, 1-piperidinyl, 4-carboxyethylpiperazinyl, 4-C<sub>1-4</sub> alkylsulfonyl piperazinyl, 4-methylpiperidinyl, 4-methoxypiperidinyl, 4-methylpiperazinyl, 3-diethylaminocarbonylpiperidinyl, or morpholinyl; and  
ring A is 2-hydroxyphenyl, 2-methoxyphenyl, or 1-pyrrolyl.

11. The compound according to claim 10, wherein:

X<sup>1</sup>, X<sup>2</sup>, and X<sup>4</sup> are CH<sub>2</sub>, and X<sup>3</sup> is N-benzyl, N-(3-methoxybenzyl), N-(4-carboxymethylbenzyl), CH<sub>2</sub>, or CH-Me;

p is 1;

R<sup>1</sup> is methyl or benzyl and R<sup>2</sup> is methyl or dimethylaminoethyl; or

R<sup>1</sup> and R<sup>2</sup> taken together form a 1-piperazinyl, 1-piperidinyl, 4-carboxyethylpiperazinyl, 4-C<sub>1-4</sub> alkylsulfonyl piperazinyl, 4-methylpiperidinyl, 4-methoxypiperidinyl, 3-diethylaminocarbonylpiperidinyl, or morpholinyl; and  
ring A is 2-hydroxyphenyl, 2-methoxyphenyl, or 1-pyrrolyl.

12. The compound according to claim 11, wherein:

$X^1$ ,  $X^2$ , and  $X^4$  are  $CH_2$ , and  $X^3$  is N-benzyl, N-(3-methoxybenzyl), N-(4-carboxymethylbenzyl), or CH-Me;

p is 1;

$R^1$  is methyl or benzyl and  $R^2$  is methyl or dimethylaminoethyl; or

$R^1$  and  $R^2$  taken together form a 4- $C_{1-4}$  alkylsulfonyl piperazinyl, 4-methylpiperidinyl, or 3-diethylaminocarbonylpiperidinyl; and

ring A is 2-hydroxyphenyl or 2-methoxyphenyl.

13. The compound according to claim 12, wherein:

$X^1$ ,  $X^2$ , and  $X^4$  are  $CH_2$ , and  $X^3$  is N-(3-methoxybenzyl) or CH-Me;

p is 1;

$R^1$  and  $R^2$  are both methyl; or

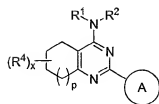
$R^1$  and  $R^2$  taken together form a 4-methylsulfonylpiperazinyl or 4-ethylsulfonylpiperazinyl; and

ring A is 2-hydroxyphenyl or 2-methoxyphenyl.

14. The compound according to claim 9, wherein:

$X^1$ ,  $X^2$ , and  $X^4$  are  $CH_2$ , and  $X^3$  is  $CH_2$  or CH-Me, p is 1,  $R^1$  and  $R^2$  each are methyl or  $R^1$  and  $R^2$  taken together form 1-piperazinyl, and ring A is 2-hydroxyphenyl or 1-pyrrolyl.

15. A compound of formula I':



I'

or a pharmaceutically acceptable salt thereof, wherein:

$R^1$  and  $R^2$  are each independently hydrogen, or an optionally substituted group selected from  $C_{1-6}$  aliphatic, a 5-6 membered aryl ring having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or  $R^1$  and  $R^2$ , taken together with the nitrogen atom to which they are bound, form an optionally substituted 3-8 membered heterocyclyl or heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein  $R^1$ ,  $R^2$ , or any ring formed by  $R^1$  and  $R^2$  taken together, are each independently optionally substituted at one or more carbon atoms with 0-4 occurrences of  $-R^5$ , and at one or more substitutable nitrogen atoms with  $-R^6$ ;

Ring A is a 5-6 membered monocyclic or 8-10 membered bicyclic aryl ring having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, optionally substituted at one or more carbon atoms with 0-5 occurrences of  $-R^7$ , and at one or more substitutable nitrogen atoms with  $-R^8$ ;

x is 0-6;

p is 0, 1, or 2; and

each occurrence of  $R^4$ ,  $R^5$ , and  $R^7$  is independently  $Q-R^x$ , wherein Q is a bond or is a  $C_1-C_6$  alkylidene chain wherein up to two non-adjacent methylene units of Q are optionally and independently replaced by CO,  $CO_2$ , COCO, CONR, OCONR, NRNR, NRNRCO, NRCO, NR $CO_2$ , NRCONR, SO,  $SO_2$ , NRSO $_2$ ,  $SO_2$ NR, NRSO $_2$ NR, O, S, or NR;

each occurrence of R is independently selected from hydrogen or an optionally substituted  $C_{1-6}$  aliphatic group;

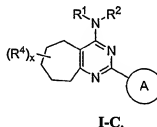
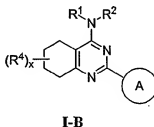
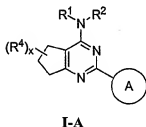
each occurrence of  $R'$  is independently selected from hydrogen or an optionally substituted group selected from  $C_{1-8}$  aliphatic,  $C_{6-10}$  aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclyl ring having 3-10 ring atoms, or wherein R and  $R'$  taken together with the atom(s) to which they are bound, or two occurrences of  $R'$  taken together with the atom(s) to which they are bound, form a 5-8 membered cycloalkyl, heterocyclyl, aryl, or heteroaryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and

each occurrence of  $R^6$  or  $R^8$  is independently  $R'$ ,  $-COR'$ ,  $-CO_2(C_{1-6}$  aliphatic),  $-CON(R')_2$ , or  $-SO_2R'$ ;

provided that:

- a) when p is 0 or 1, then at least one  $R^4$  is other than hydrogen;
- b) when Ring A is a substituted or unsubstituted piperizinyl group, then at least one  $R^4$  is other than hydrogen;
- c) when  $R^1$  is hydrogen and  $R^2$  is 1H-indazol-3-yl, 7-fluoro-1H-indazol-3-yl, 5-fluoro-1H-indazol-3-yl, 5,7-difluoro-1H-indazol-3-yl or 5-methyl-1H-pyrazolyl, and Ring A is an unsubstituted phenyl group or is a phenyl group substituted in the ortho position with Cl or  $CF_3$ , then at least one  $R^4$  is other than hydrogen; and
- d) 5(6H)-quinazolinone, 4-anilino-7,8-dihydro-2,7-diphenyl- and 5(6H)-quinazolinone, 4-anilino-7,8-dihydro-7,7-dimethyl-2-phenyl- are excluded.

16. The compound according to claim 15, wherein said compound has formula I-A, I-B, or I-C:



17. The compound according to claim 16, having formula I-B.

18. The compound according to claim 17, wherein:

(i) ring A is pyrrolyl, pyridyl, fluorophenyl, hydroxyphenyl, acyloxyphenyl, hydroxy-fluorophenyl, methoxyphenyl, phenyl-phosphate disodium salt, methylpiperidyl, ethyl-carbamic acid phenyl ester;

(ii) x is 0-2, and  $R^4$  is  $C_{1-4}$  alkyl optionally substituted with hydroxy,  $C_{1-4}$  alkoxy, or halo, hydroxy,  $C_{1-4}$  alkylcarbonyloxy or carbo( $C_{1-4}$ alkoxy);

(iii)  $R^1$  is hydrogen,  $C_{1-4}$  alkyl, or benzyl, and  $R^2$  is  $C_{1-4}$  alkyl, di( $C_{1-4}$  alkyl)amino- $C_{1-4}$  alkyl, 2-(2'-tetrahydrofuranyl)methyl, 2-hydroxy-1-methyl-ethyl, or imidazol-5-yl-ethyl; or

(iv)  $R^1$  and  $R^2$  taken together form a ring selected from N-pyrrolidinyl, N-piperidinyl, N-piperazinyl, morpholinyl, thiomorpholinyl, ( $C_{1-4}$  alkyl)sulfonylpiperazinyl, wherein said ring is optionally substituted with up to 3 substituents selected from halo, oxo, hydroxy, trifluoromethyl,

-O- C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkyl optionally substituted with hydroxy, amino, aminocarbonyl, di(C<sub>1-4</sub>alkyl)aminocarbonyl, or carboxy.

19. The compound according to claim 17, wherein:

(i) ring A is 1-pyrrolyl, 2-pyridyl, 2-fluorophenyl, 2-hydroxyphenyl, 2-acyloxyphenyl, 2-hydroxy-6-fluorophenyl, 2-methoxyphenyl, phenyl-2-phosphate disodium salt, or 4-methylpiperidyl, 2-ethyl-carbamic acid phenyl ester

(ii) x is 0, or x is 1 and R<sup>4</sup> is 6-methyl, 7-methyl, 8-hydroxy, or 2-t-butylcarbonyloxy, or x is 2, and R<sup>4</sup> is 6-carboxymethyl and 7-carboxymethyl;

(iii) R<sup>1</sup> is hydrogen, methyl, ethyl, or benzyl, and R<sup>2</sup> is methyl, ethyl, dimethylaminoethyl, 2-(2'-tetrahydrofuranyl)methyl, 2-hydroxy-1-methyl-ethyl, methylaminoethyl, imidazol-5-yl-ethyl, or

(vii) R<sup>1</sup> and R<sup>2</sup> taken together form 4-methoxypiperidinyl, N-pyrrolidinyl, 3-trifluoromethyl-1-pyrrolidinyl, 4-butylsulfonyl-piperazinyl, 1-piperidinyl, 1-piperazinyl, 4-methylpiperidinyl, 4-hydroxypiperidinyl, 4-morpholinyl, 4-methylsulfonylpiperazinyl, 4-ethylsulfonylpiperazinyl, 4-isopropylsulfonylpiperazinyl, N-piperidinyl, 3-diethylaminocarbonyl-1-piperidinyl, 4-oxo-piperidinyl, 3-aminocarbonyl-piperidinyl, 4-methylpiperazinyl, or 4-carboxyethyl-piperazinyl.

20. The compound according to claim 17, wherein:

(i) ring A is 2-pyridyl, 2-fluorophenyl, 2-hydroxyphenyl, 2-acyloxyphenyl, 2-hydroxy-6-fluorophenyl, 2-methoxyphenyl, or 4-methylpiperidyl,

(ii) x is 0, or x is 1 and R<sup>4</sup> is 6-methyl, 7-methyl, or 8-hydroxy,

(iii) R<sup>1</sup> is methyl, ethyl, or benzyl, and R<sup>2</sup> is methyl, ethyl, dimethylaminoethyl, or 2-(2'-tetrahydrofuranyl)methyl, or R<sup>1</sup> and R<sup>2</sup> taken together form 4-methoxypiperidinyl, N-pyrrolidinyl, 4-butylsulfonyl-piperazinyl, piperidinyl, 4-methylpiperidinyl, 4-hydroxypiperidinyl, 4-morpholinyl, 4-methylsulfonylpiperazinyl, 4-ethylsulfonylpiperazinyl, N-piperidinyl, 3-diethylaminocarbonyl-1-piperidinyl, or 4-carboxyethyl-piperazinyl.

21. The compound according to claim 17, wherein:

(i) ring A is 2-pyridyl, 2-hydroxyphenyl, 2-acyloxyphenyl, 2-hydroxy-6-fluorophenyl, or 4-methylpiperidyl;

(ii) x is 0, or x is 1 and R<sup>4</sup> is 7-methyl;

(iii) R<sup>1</sup> is methyl and R<sup>2</sup> is methyl or 2-(2'-tetrahydrofuran-yl)methyl, or R<sup>1</sup> and R<sup>2</sup> taken together form 4-butylsulfonyl-piperazinyl, piperidinyl, 4-methylpiperidinyl, 4-morpholinyl, 4-methylsulfonylpiperazinyl, 4-ethylsulfonylpiperazinyl, 4-piperidinyl, or 4-carboxyethyl-piperazinyl.

22. The compound according to claim 17, wherein:

ring A is 2-hydroxyphenyl, R<sup>1</sup> and R<sup>2</sup>, taken together, form a 1-piperidinyl ring, x is 1, and R<sup>4</sup> is 7-methyl.

23. The compound according to claim 15 or 16, wherein neither R<sup>1</sup> nor R<sup>2</sup> is hydrogen, and R<sup>1</sup> and R<sup>2</sup> are each independently selected from a 5- or 6-membered aryl ring having 0-5 heteroatoms independently selected from N, O, or S, a 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from N, O, or S, or an optionally substituted C<sub>1-4</sub> aliphatic group, wherein one or more methylene units in the C<sub>1-4</sub> aliphatic group are optionally and independently replaced with NR, O, (CO)O, O(CO), NR(CO), (CO)NR, SO<sub>2</sub>(NR), or (NR)SO<sub>2</sub>.

24. The compound according to claim 23, wherein R<sup>1</sup> and R<sup>2</sup> are each independently an optionally substituted C<sub>1-4</sub> aliphatic group, wherein one or more methylene units in the C<sub>1-4</sub> aliphatic group are optionally and independently replaced with NR, O, (CO)O, O(CO), NR(CO), (CO)NR, SO<sub>2</sub>(NR), or (NR)SO<sub>2</sub>.

25. The compound according to claim 24, wherein when R<sup>1</sup> and R<sup>2</sup> are each independently an optionally substituted C<sub>1-4</sub> aliphatic group, wherein one or more methylene units in the C<sub>1-4</sub> aliphatic group are optionally and independently replaced with NR, O, (CO)O, O(CO), NR(CO), (CO)NR, SO<sub>2</sub>(NR), or (NR)SO<sub>2</sub>.

26. The compound according to claim 25,  $R^1$  and  $R^2$  groups are each independently optionally substituted methyl, ethyl, cyclopropyl, n-propyl, propenyl, cyclobutyl,  $(CO)OCH_2CH_3$ ,  $(CH_2)_2OCH_3$ ,  $CH_2(CO)OCH_2CH_3$ ,  $CH_2(CO)OCH_3$ ,  $CH(CH_3)CH_2CH_3$ , or t-butyl, or n-butyl.

27. The compound according to claim 15 or 16, wherein:

(i) one of  $R^1$  or  $R^2$  is hydrogen and the other of  $R^1$  or  $R^2$  is a 5-6 membered aryl ring having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or

(ii) one of  $R^1$  or  $R^2$  is hydrogen, and the other of  $R^1$  or  $R^2$  is an optionally substituted  $C_{1-4}$  aliphatic group, wherein one or more methylene units in the  $C_{1-4}$  aliphatic group are optionally and independently replaced with NR, O,  $(CO)O$ ,  $O(CO)$ ,  $NR(CO)$ ,  $(CO)NR$ ,  $SO_2(NR)$ , or  $(NR)SO_2$ .

28. The compound according to claim 23, wherein  $R^1$  or  $R^2$  is selected from:



a



b



c



d



e



f



g



h



i



j



k



l





**m****n****o****p****q****r****s****t****u****v****w****x****y****z****aa****bb.**

29. The compound according to claim 15 or 16, wherein  $R^1$  and  $R^2$ , taken together with the nitrogen atom to which they are bound, form an optionally substituted 3-8 membered heterocyclyl ring having 1-3 heteroatoms independently selected from nitrogen or oxygen.

30. The compound according to claim 29,  $R^1$  and  $R^2$  are taken together with the nitrogen atom to which they are bound and form a ring selected from:

**cc****dd****ee****ff****gg****hh.**

31. The compound according to claim 30, wherein  $R^1$  and  $R^2$  taken together are optionally substituted pyrrolidin-1-yl (ff), piperidin-1-yl (dd), piperazin-1-yl (cc), or morpholin-4-yl (ee).

32. The compound according to claim 31, wherein  $z$  is 0-2.

33. The compound according to claim 31, wherein  $z$  is 0.

34. The compound according to claim 30, wherein  $R^5$  is independently selected from halogen, CN,  $NO_2$ , or an optionally substituted group selected from  $C_{1-6}$  alkyl, aryl, aryl( $C_{1-6}$ )alkyl,  $-N(R')_2$ ,  $-CH_2N(R')_2$ ,  $OR'$ ,  $-CH_2OR'$ ,  $SR'$ ,  $-CH_2SR'$ ,  $COOR'$ ,  $-NRCOR'$ ,  $-(CH_2)_2N(R')_2$ ,  $-(CH_2)_2OR'$ ,  $-(CH_2)_2SR'$ ,  $-COR'$ ,  $-CON(R')_2$ , or  $-S(O)_2N(R')_2$ .

35. The compound according to claim 34, wherein  $R^5$  is independently selected from Cl, Br, F,  $CF_3$ , Me, Et, CN,  $NO_2$ ,  $-COOH$ ,  $NH_2$ ,  $-N(CH_3)_2$ ,  $-N(Et)_2$ ,  $-N(iPr)_2$ ,  $-O(CH_2)_2OCH_3$ ,  $-CONH_2$ ,  $-COOCH_3$ ,  $-OH$ ,  $-CH_2OH$ ,  $-NHC(=O)CH_3$ ,  $-SO_2NH_2$ ,  $SO_2N(CH_3)_2$ , piperidinyl, piperizinyl, morpholino, or an optionally substituted group selected from  $C_{1-4}$  alkoxy, phenyl, phenyloxy, benzyl, or benzyloxy.

36. The compound according to claim 28, wherein  $R^6$  is independently selected from hydrogen, or an optionally substituted group selected from  $C_{1-6}$  alkyl, aryl, aryl( $C_{1-6}$ )alkyl,  $-N(R')_2$ ,  $-CH_2N(R')_2$ ,  $-CH_2OR'$ ,  $-CH_2SR'$ ,  $-(CH_2)_2N(R')_2$ ,  $-(CH_2)_2OR'$ ,  $-(CH_2)_2SR'$ ,  $-COR'$ ,  $-CON(R')_2$ , or  $-S(O)_2N(R')_2$ .

37. The compound according to claim 36, wherein  $R^6$  is independently selected from H, Me,  $CF_3$ , ethyl, propyl, butyl, pentyl,  $CO(C_{1-4}alkyl)$ ,  $-CONH_2$ ,  $-COO(C_{1-4}alkyl)$ ,  $-CH_2OH$ ,  $-SO_2NH_2$ ,  $SO_2N(CH_3)_2$ , or optionally substituted phenyl.

38. The compound according to claim 15 or 16, wherein:

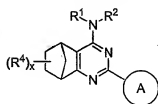
$x$  is 0, 1, or 2; and

each  $R^4$  independently hydrogen, halogen, CN,  $NO_2$ , or an optionally substituted group selected from  $C_{1-6}$  alkyl, aryl, aryl( $C_{1-6}$ )alkyl,  $-N(R')_2$ ,  $-CH_2N(R')_2$ ,  $OR'$ ,  $-CH_2OR'$ ,  $SR'$ ,  $-CH_2SR'$ ,  $COOR'$ ,  $-NRCOR'$ ,  $-(CH_2)_2N(R')_2$ ,  $-(CH_2)_2OR'$ ,  $-(CH_2)_2SR'$ ,  $-COR'$ ,  $-CON(R')_2$ , or  $-S(O)_2N(R')_2$ .

39. The compound according to claim 38, wherein each  $R^4$  is independently H, Cl, Br, F,  $CF_3$ , Me, Et, CN,  $NO_2$ ,  $-COOH$ ,  $NH_2$ ,  $-N(CH_3)_2$ ,  $-N(Et)_2$ ,  $-N(iPr)_2$ ,  $-O(CH_2)_2OCH_3$ ,  $-CONH_2$ ,  $-COOCH_3$ ,  $-OH$ ,  $-CH_2OH$ ,  $-NHCOCH_3$ ,  $-SO_2NH_2$ ,  $SO_2N(CH_3)_2$ , piperidinyl, piperizinyl, morpholino, or an optionally substituted group selected from  $C_{1-4}$  alkoxy, phenyl, phenyloxy, benzyl, or benzyloxy.

40. The compound according to claim 15 or 16, wherein two occurrences of  $R^4$ , taken together form an optionally substituted 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

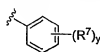
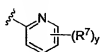
41. The compound according to claim 15 or 16, two occurrences of  $R^4$ , taken together form a cycloalkyl group and compounds have the structure as shown in formula I-B-i:



**I-B-i.**

42. The compound according to claim 15 or 16, wherein Ring A is a phenyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, pyrrolyl, piperidinyl, indolyl, indazolyl, benzotriazolyl, pyrazolyl, benzopyrazolyl, imidazolyl, benzimidazolyl, thiazolyl, benzthiazolyl, oxazolyl, benzoxazolyl, isoxazolyl, benzisoxazolyl, isothiazolyl, benzisothiazolyl, triazolyl, benzotriazolyl, thiadiazolyl, thienyl, benzothienyl, furanoyl, benzofuranoyl, or triazinyl ring, each optionally substituted at one or more carbon atoms with 0-5 occurrences of  $-R^7$ , and at one or more substitutable nitrogen atoms with  $-R^8$ .

43. The compound according to claim 15 or 16, wherein Ring A is optionally substituted phenyl, 2-pyridyl, 3-pyridyl, or 4-pyridyl:

**a****b****c****d**

wherein each y is independently 0-5.

44. The compound according to claim 43, wherein y is 0-2.

45. The compound according to claim 44, wherein y is 0 and Ring A is unsubstituted.

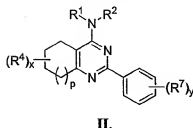
46. The compound according to claim 15 or 16, wherein  $R^7$  groups are independently hydrogen, halogen, CN,  $\text{NO}_2$ , or an optionally substituted group selected from  $\text{C}_{1-6}$  alkyl, aryl, aryl( $\text{C}_{1-6}$ )alkyl,  $-\text{N}(\text{R}')_2$ ,  $-\text{CH}_2\text{N}(\text{R}')_2$ ,  $\text{OR}'$ ,  $-\text{CH}_2\text{OR}'$ ,  $\text{SR}'$ ,  $-\text{CH}_2\text{SR}'$ ,  $\text{COOR}'$ ,  $-\text{NRCOR}'$ ,  $-(\text{CH}_2)_2\text{N}(\text{R}')_2$ ,  $-(\text{CH}_2)_2\text{OR}'$ ,  $-(\text{CH}_2)_2\text{SR}'$ ,  $-\text{COR}'$ ,  $-\text{CON}(\text{R}')_2$ , or  $-\text{S}(\text{O})_2\text{N}(\text{R}')_2$ .

47. The compound according to claim 46, wherein  $\text{R}^7$  is independently H, Cl, Br, F,  $\text{CF}_3$ , Me, Et, CN,  $\text{NO}_2$ ,  $-\text{COOH}$ ,  $\text{NH}_2$ ,  $-\text{N}(\text{CH}_3)_2$ ,  $-\text{N}(\text{Et})_2$ ,  $-\text{N}(\text{iPr})_2$ ,  $-\text{O}(\text{CH}_2)_2\text{OCH}_3$ ,  $-\text{CONH}_2$ ,  $-\text{COOCH}_3$ ,  $-\text{OH}$ ,  $-\text{CH}_2\text{OH}$ ,  $-\text{NHCOCH}_3$ ,  $-\text{SO}_2\text{NH}_2$ ,  $\text{SO}_2\text{N}(\text{CH}_3)_2$ , piperidiny, piperiziny, morpholino, or an optionally substituted group selected from  $\text{C}_{1-4}$  alkoxy, phenyl, phenyloxy, benzyl, or benzyloxy.

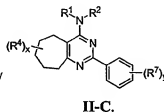
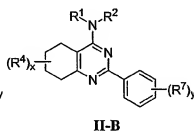
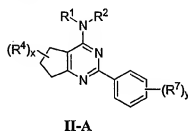
48. The compound according to claim 15 or 16,  $\text{R}^8$  is independently hydrogen, or an optionally substituted group selected from  $\text{C}_{1-6}$  alkyl, aryl, aryl( $\text{C}_{1-6}$ )alkyl,  $-\text{N}(\text{R}')_2$ ,  $-\text{CH}_2\text{N}(\text{R}')_2$ ,  $-\text{CH}_2\text{OR}'$ ,  $-\text{CH}_2\text{SR}'$ ,  $-(\text{CH}_2)_2\text{N}(\text{R}')_2$ ,  $-(\text{CH}_2)_2\text{OR}'$ ,  $-(\text{CH}_2)_2\text{SR}'$ ,  $-\text{COR}'$ ,  $-\text{CON}(\text{R}')_2$ , or  $-\text{S}(\text{O})_2\text{N}(\text{R}')_2$ .

49. The compound according to claim 48,  $\text{R}^8$  is independently H, Me,  $\text{CF}_3$ , ethyl, propyl, butyl, pentyl,  $\text{CO}(\text{C}_{1-4}$  alkyl),  $-\text{CONH}_2$ ,  $-\text{COO}(\text{C}_{1-4}$  alkyl),  $-\text{CH}_2\text{OH}$ ,  $-\text{SO}_2\text{NH}_2$ ,  $\text{SO}_2\text{N}(\text{CH}_3)_2$ , or optionally substituted phenyl.

50. A compound according to claim 15, having formula II:



51. The compound according to claim 50, having formula II-A, formula II-B, or formula II-C:



52. The compound according to claim 51, wherein neither  $R^1$  nor  $R^2$  is hydrogen, and  $R^1$  and  $R^2$  are each independently selected from a 5- or 6-membered aryl ring having 0-5 heteroatoms independently selected from N, O, or S; a 3-7 membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from N, O, or S, or an optionally substituted  $C_{1-4}$  aliphatic group, wherein one or more methylene units in the  $C_{1-4}$  aliphatic group are optionally and independently replaced with NR, O, (CO)O, O(CO), NR(CO), (CO)NR,  $SO_2$ (NR), or (NR) $SO_2$ .

53. The compound according to claim 51, wherein both  $R^1$  and  $R^2$  are an optionally substituted  $C_{1-4}$  aliphatic group, wherein one or more methylene units in the  $C_{1-4}$  aliphatic group are optionally and independently replaced with NR, O, (CO)O, O(CO), NR(CO), (CO)NR,  $SO_2$ (NR), or (NR) $SO_2$ .

54. The compound according to claim 53, wherein  $R^1$  and  $R^2$  are an optionally substituted  $C_{1-4}$  aliphatic group, wherein one or more methylene units in the  $C_{1-4}$  aliphatic group

are optionally and independently replaced with NR, O, (CO)O, O(CO), NR(CO), (CO)NR, SO<sub>2</sub>(NR), or (NR)SO<sub>2</sub>.

55. The compound according to claim 54, wherein R<sup>1</sup> and R<sup>2</sup> are optionally substituted methyl, ethyl, cyclopropyl, n-propyl, propenyl, cyclobutyl, (CO)OCH<sub>2</sub>CH<sub>3</sub>, (CH<sub>2</sub>)<sub>2</sub>OCH<sub>3</sub>, CH<sub>2</sub>(CO)OCH<sub>2</sub>CH<sub>3</sub>, CH<sub>2</sub>(CO)OCH<sub>3</sub>, CH(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>3</sub>, or t-butyl, or n-butyl.

56. The compound according to claim 51, wherein one of R<sup>1</sup> or R<sup>2</sup> is hydrogen and the other of R<sup>1</sup> or R<sup>2</sup> is a 5-6 membered aryl ring having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

57. The compound according to claim 51, wherein one of R<sup>1</sup> or R<sup>2</sup> is hydrogen, and the other of R<sup>1</sup> or R<sup>2</sup> is an optionally substituted C<sub>1-4</sub> aliphatic group, wherein one or more methylene units in the C<sub>1-4</sub> aliphatic group are optionally and independently replaced with NR, O, (CO)O, O(CO), NR(CO), (CO)NR, SO<sub>2</sub>(NR), or (NR)SO<sub>2</sub>.

58. The compound according to claim 51, wherein R<sup>1</sup> or R<sup>2</sup> is selected from:



a



b



c



d



e



f



g



h



i



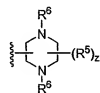
j



k



l

**m****n****o****p****q****r****s****t****u****v****w****x****y****z****aa****bb**

wherein each  $z$  is independently 0-4.

59. The compound according to claim 51, wherein  $R^1$  and  $R^2$ , taken together with the nitrogen atom to which they are bound, form an optionally substituted 3-8 membered heterocyclyl ring having 1-3 heteroatoms independently selected from nitrogen or oxygen.

60. The compound according to claim 59, wherein  $R^1$  and  $R^2$  are taken together form a ring selected from:

**cc****dd****ee**

**ff****gg****hh**

wherein each z is independently 0-4.

61. The compound according to claim 60, wherein  $R^1$  and  $R^2$  taken together are optionally substituted pyrrolidin-1-yl (**ff**), piperidin-1-yl (**dd**), piperazin-1-yl (**cc**), or morpholin-4-yl (**ee**).

62. The compound according to claim 61, wherein z is 0-2.

63. The compound according to claim 62, wherein z is 0 and the ring is unsubstituted.

64. The compound according to claim 61, wherein  $R^5$  is independently halogen, CN,  $NO_2$ , or an optionally substituted group selected from  $C_{1-6}$  alkyl, aryl,  $aryl(C_{1-6})alkyl$ ,  $-N(R')_2$ ,  $-CH_2N(R')_2$ ,  $OR'$ ,  $-CH_2OR'$ ,  $SR'$ ,  $-CH_2SR'$ ,  $COOR'$ ,  $-NRCOR'$ ,  $-(CH_2)_2N(R')_2$ ,  $-(CH_2)_2OR'$ ,  $-(CH_2)_2SR'$ ,  $-COR'$ ,  $-CON(R')_2$ , or  $-S(O)_2N(R')_2$ .

65. The compound according to claim 64, wherein  $R^5$  is independently Cl, Br, F,  $CF_3$ , Me, Et, CN,  $NO_2$ ,  $-COOH$ ,  $NH_2$ ,  $-N(CH_3)_2$ ,  $-N(Et)_2$ ,  $-N(iPr)_2$ ,  $-O(CH_2)_2OCH_3$ ,  $-CONH_2$ ,  $-COOCH_3$ ,  $-OH$ ,  $-CH_2OH$ ,  $-NHCOCH_3$ ,  $-SO_2NH_2$ ,  $SO_2N(CH_3)_2$ , piperidinyl, piperizinyl, morpholino, or an optionally substituted group selected from  $C_{1-4}$  alkoxy, phenyl, phenyloxy, benzyl, or benzyloxy.

66. The compound according to claim 51, wherein  $R^6$  is independently hydrogen, or an optionally substituted group selected from  $C_{1-6}$  alkyl, aryl,  $aryl(C_{1-6})alkyl$ ,  $-N(R')_2$ ,  $-CH_2N(R')_2$ ,  $-CH_2OR'$ ,  $-CH_2SR'$ ,  $-(CH_2)_2N(R')_2$ ,  $-(CH_2)_2OR'$ ,  $-(CH_2)_2SR'$ ,  $-COR'$ ,  $-CON(R')_2$ , or  $-S(O)_2N(R')_2$ .



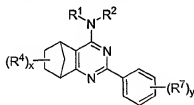
67. The compound according to claim 66, wherein  $R^6$  is independently H, Me,  $CF_3$ , ethyl, propyl, butyl, pentyl,  $CO(C_1-C_4 \text{ alkyl})$ ,  $-CONH_2$ ,  $-COO(C_1-C_4 \text{ alkyl})$ ,  $-CH_2OH$ ,  $-SO_2NH_2$ ,  $SO_2N(CH_3)_2$ , or optionally substituted phenyl.

68. The compound according to claim 51, wherein x is 0, 1, or 2 and each  $R^4$  is independently hydrogen, halogen, CN,  $NO_2$ , or an optionally substituted group selected from  $C_{1-6}$  alkyl, aryl, aryl( $C_{1-6}$ alkyl),  $-N(R')_2$ ,  $-CH_2N(R')_2$ ,  $OR'$ ,  $-CH_2OR'$ ,  $SR'$ ,  $-CH_2SR'$ ,  $COOR'$ ,  $-NRCOR'$ ,  $-(CH_2)_2N(R')_2$ ,  $-(CH_2)_2OR'$ ,  $-(CH_2)_2SR'$ ,  $-COR'$ ,  $-CON(R')_2$ , or  $-S(O)_2N(R')_2$ .

69. The compound according to claim 51, wherein each  $R^3$  is independently H, Cl, Br, F,  $CF_3$ , Me, Et, CN,  $NO_2$ ,  $-COOH$ ,  $NH_2$ ,  $-N(CH_3)_2$ ,  $-N(Et)_2$ ,  $-N(iPr)_2$ ,  $-O(CH_2)_2OCH_3$ ,  $-CONH_2$ ,  $-COOCH_3$ ,  $-OH$ ,  $-CH_2OH$ ,  $-NHCOCH_3$ ,  $-SO_2NH_2$ ,  $SO_2N(CH_3)_2$ , piperidinyl, piperiziny, morpholino, or an optionally substituted group selected from  $C_{1-4}$  alkoxy, phenyl, phenyloxy, benzyl, or benzyloxy.

70. The compound according to claim 51, wherein two occurrences of  $R^4$ , taken together form an optionally substituted 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

71. The compound according to claim 70, wherein two occurrences of  $R^4$ , taken together form a cycloalkyl group to form compound of formula II-B-i:



II-B-i.

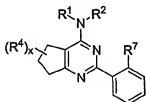
72. The compound according to claim 51, wherein y is 0-2.

73. The compound according to claim 72, wherein y is 0 and Ring A is unsubstituted.

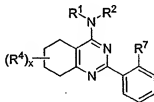
74. The compound according to claim 51, wherein  $R^7$  is independently hydrogen, halogen, CN,  $NO_2$ , or an optionally substituted group selected from  $C_{1-6}$  alkyl, aryl, aryl( $C_{1-6}$ )alkyl,  $-N(R')_2$ ,  $-CH_2N(R')_2$ ,  $OR'$ ,  $-CH_2OR'$ ,  $SR'$ ,  $-CH_2SR'$ ,  $COOR'$ ,  $-NRCOR'$ ,  $-(CH_2)_2N(R')_2$ ,  $-(CH_2)_2OR'$ ,  $-(CH_2)_2SR'$ ,  $-COR'$ ,  $-CON(R')_2$ , or  $-S(O)_2N(R')_2$ .

75. The compound according to claim 74, wherein  $R^7$  is independently H, Cl, Br, F,  $CF_3$ , Me, Et, CN,  $NO_2$ ,  $-COOH$ ,  $NH_2$ ,  $-N(CH_3)_2$ ,  $-N(Et)_2$ ,  $-N(iPr)_2$ ,  $-O(CH_2)_2OCH_3$ ,  $-CONH_2$ ,  $-COOCH_3$ ,  $-OH$ ,  $-CH_2OH$ ,  $-NHCOCH_3$ ,  $-SO_2NH_2$ ,  $SO_2N(CH_3)_2$ , piperidinyl, piperiziny, morpholino, or an optionally substituted group selected from  $C_{1-4}$  alkoxy, phenyl, phenyloxy, benzyl, or benzyloxy.

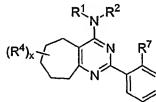
76. The compound according to any one of claims 51 to 75, having formula III-A, formula III-B, or formula III-C:



III-A



III-B



III-C

wherein each  $R^7$  is independently halogen, CN,  $NO_2$ , or an optionally substituted group selected from  $C_{1-4}$  alkyl, aryl, aralkyl,  $-N(R')_2$ ,  $-CH_2N(R')_2$ ,  $-OR'$ ,  $-CH_2OR'$ ,  $-SR'$ ,  $-CH_2SR'$ ,  $-COOR'$ ,  $-NRCOR'$ ,  $-CON(R')_2$ , or  $-S(O)_2N(R')_2$ .

77. The compound according to claim 76, having formula III-B.

78. The compound according to claim 76, having formula III-A.

79. The compound according to claim 78, wherein:

$x$  is 0,  $R^7$  is hydroxy,  $R^1$  and  $R^2$  are both  $C_{1-4}$  alkyl, or  $R^1$  and  $R^2$ , taken together, form a pyrrolidyl, piperidinyl, or morpholinyl ring.

80. The compound according to claim 79, wherein  $x$  is 0,  $R^7$  is hydroxy,  $R^1$  and  $R^2$  are both methyl, or  $R^1$  and  $R^2$ , taken together, form a pyrrolidyl or piperidinyl ring.

81. The compound according to claim 80, wherein x is 0, R<sup>7</sup> is hydroxy, R<sup>1</sup> and R<sup>2</sup> are both methyl, or R<sup>1</sup> and R<sup>2</sup>, taken together, form a pyrrolidyl ring.

82. The compound according to claim 76, wherein:

- a) R<sup>1</sup> and R<sup>2</sup> are each independently selected from a 5- or 6-membered aryl ring having 0-5 heteroatoms independently selected from N, O, or S, a 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from N, O, or S, or an optionally substituted C<sub>1-4</sub> aliphatic group, wherein one or more methylene units in the C<sub>1-4</sub> aliphatic group are optionally and independently replaced with NR, O, (CO)O, O(CO), NR(CO), (CO)NR, SO<sub>2</sub>(NR), or (NR)SO<sub>2</sub>; and
- b) x is 0, 1, or 2, and R<sup>4</sup> is hydrogen, halogen, CN, NO<sub>2</sub>, or an optionally substituted group selected from C<sub>1-6</sub> alkyl, aryl, aryl(C<sub>1-6</sub>)alkyl, -N(R')<sub>2</sub>, -CH<sub>2</sub>N(R')<sub>2</sub>, OR', -CH<sub>2</sub>OR', SR', -CH<sub>2</sub>SR', COOR', -NRCOR', -(CH<sub>2</sub>)<sub>2</sub>N(R')<sub>2</sub>, -(CH<sub>2</sub>)<sub>2</sub>OR', -(CH<sub>2</sub>)<sub>2</sub>SR', -COR', -CON(R')<sub>2</sub>, or -S(O)<sub>2</sub>N(R')<sub>2</sub>.

83. The compound according to claim 76, wherein:

- a) R<sup>1</sup> and R<sup>2</sup> are each independently optionally substituted methyl, ethyl, cyclopropyl, n-propyl, propenyl, cyclobutyl, (CO)OCH<sub>2</sub>CH<sub>3</sub>, (CH<sub>2</sub>)<sub>2</sub>OCH<sub>3</sub>, CH<sub>2</sub>(CO)OCH<sub>2</sub>CH<sub>3</sub>, CH<sub>2</sub>(CO)OCH<sub>3</sub>, CH(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>3</sub>, or t-butyl, or n-butyl; and
- b) x is 0, 1, or 2, and each R<sup>4</sup> is independently H, Cl, Br, F, CF<sub>3</sub>, Me, Et, CN, NO<sub>2</sub>, -COOH, NH<sub>2</sub>, -N(CH<sub>3</sub>)<sub>2</sub>, -N(Et)<sub>2</sub>, -N(iPr)<sub>2</sub>, -O(CH<sub>2</sub>)<sub>2</sub>OCH<sub>3</sub>, -CONH<sub>2</sub>, -COOCH<sub>3</sub>, -OH, -CH<sub>2</sub>OH, -NHCOCH<sub>3</sub>, -SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, piperidinyl, piperizinyl, morpholino, or an optionally substituted group selected from C<sub>1-4</sub> alkoxy, phenyl, phenyloxy, benzyl, or benzyloxy.

84. The compound according to claim 76, wherein:

- a) R<sup>1</sup> and R<sup>2</sup> are each independently optionally substituted methyl, ethyl, cyclopropyl, n-propyl, propenyl, cyclobutyl, (CO)OCH<sub>2</sub>CH<sub>3</sub>, (CH<sub>2</sub>)<sub>2</sub>OCH<sub>3</sub>, CH<sub>2</sub>(CO)OCH<sub>2</sub>CH<sub>3</sub>, CH<sub>2</sub>(CO)OCH<sub>3</sub>, CH(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>3</sub>, or t-butyl, or n-butyl;

b)  $x$  is 0, 1, or 2, and each  $R^4$  is independently H, Cl, Br, F,  $CF_3$ , Me, Et, CN,  $NO_2$ ,  $-COOH$ ,  $NH_2$ ,  $-N(CH_3)_2$ ,  $-N(Et)_2$ ,  $-N(iPr)_2$ ,  $-O(CH_2)_2OCH_3$ ,  $-CONH_2$ ,  $-COOCH_3$ ,  $-OH$ ,  $-CH_2OH$ ,  $-NHCOCH_3$ ,  $-SO_2NH_2$ ,  $SO_2N(CH_3)_2$ , piperidinyl, piperizinyl, morpholino, or an optionally substituted group selected from  $C_{1-4}$  alkoxy, phenyl, phenyloxy, benzyl, or benzyloxy; and

c)  $R^7$  is Cl, Br, F,  $CF_3$ , Me, Et, CN,  $NO_2$ ,  $-COOH$ ,  $NH_2$ ,  $-N(CH_3)_2$ ,  $-N(Et)_2$ ,  $-N(iPr)_2$ ,  $-O(CH_2)_2OCH_3$ ,  $-CONH_2$ ,  $-COOCH_3$ ,  $-OH$ ,  $-CH_2OH$ ,  $-NHCOCH_3$ ,  $-SO_2NH_2$ ,  $SO_2N(CH_3)_2$ , piperidinyl, piperizinyl, morpholino, or an optionally substituted group selected from  $C_{1-4}$  alkoxy, phenyl, phenyloxy, benzyl, or benzyloxy.

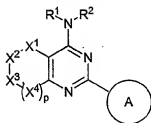
85. The compound according to claim 76 having formula III-C:

(i)  $R^7$  is hydroxy;

(ii)  $R^1$  and  $R^2$  are both  $C_{1-4}$  alkyl, preferably, methyl, or  $R^1$  and  $R^2$ , taken together, form a pyrrolinyl ring or morpholinyl ring; and

(iii)  $x$  is 0.

86. The compound according to claim 1, having formula IV:



#### IV

or a pharmaceutically acceptable salt thereof, wherein:

$p$  is 0, 1 or 2;

$X^1, X^2, X^3$  and  $X^4$  are each independently selected from  $NR^3$ ,  $C=O$ ,  $CHR^4$ , S, O,  $S=O$ , or  $SO_2$ , as valency and stability permit, provided that that  $X^1, X^2, X^3$  and  $X^4$  are not each simultaneously  $CHR^4$ ;

$R^1$  and  $R^2$  are each independently hydrogen, or an optionally substituted group selected from  $C_{1-6}$  aliphatic, a 5-6 membered aryl ring having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 3-7-membered saturated or partially unsaturated ring

having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or  $R^1$  and  $R^2$ , taken together with the nitrogen atom to which they are bound, form an optionally substituted 3-8 membered heterocyclyl or heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein  $R^1$ ,  $R^2$ , or any ring formed by  $R^1$  and  $R^2$  taken together, are each independently optionally substituted at one or more carbon atoms with 0-4 occurrences of  $-R^5$ , and at one or more substitutable nitrogen atoms with  $-R^6$ ;

Ring A is a 5-6 membered monocyclic or 8-10 membered bicyclic aryl ring having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, optionally substituted at one or more carbon atoms with 0-5 occurrences of  $-R^7$ , and at one or more substitutable nitrogen atoms with  $-R^8$ ;

each occurrence of  $R^4$ ,  $R^5$ , and  $R^7$  is independently  $Q-R^X$ ; wherein Q is a bond or is a  $C_{1-6}$  alkylidene chain wherein up to two non-adjacent methylene units of Q are optionally and independently replaced by CO,  $CO_2$ , COCO, CONR, OCONR, NRNR, NRNRCO, NRCO,  $NRCO_2$ , NRCONR, SO,  $SO_2$ ,  $NRSO_2$ ,  $SO_2NR$ ,  $NRSO_2NR$ , O, S, or NR;

each occurrence of  $R^X$  is independently selected from  $R^1$ , halogen,  $NO_2$ , or CN;

each occurrence of R is independently selected from hydrogen or an optionally substituted  $C_{1-6}$  aliphatic group;

each occurrence of  $R'$  is independently selected from hydrogen or an optionally substituted group selected from  $C_{1-8}$  aliphatic,  $C_{6-10}$  aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclyl ring having 3-10 ring atoms, or wherein R and  $R'$  taken together with the atom(s) to which they are bound, or two occurrences of  $R'$  taken together with the atom(s) to which they are bound, form a 5-8 membered cycloalkyl, heterocyclyl, aryl, or heteroaryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and

each occurrence of  $R^3$ ,  $R^6$  or  $R^8$  is independently  $R'$ ,  $-COR'$ ,  $-CO_2(C_{1-6} \text{ aliphatic})$ ,  $-CON(R')_2$ , or  $-SO_2R'$ ;

provided that:

- $R^1$  is not hydrogen when  $R^2$  is optionally substituted indazol-3-yl;
- $R^1$  is not hydrogen when  $R^2$  is optionally substituted pyrazol-3-yl;
- $R^1$  is not hydrogen when  $R^2$  is 1,2,4-triazol-3-yl;
- when p is 1, then:

- i) when  $R^1$  and  $R^2$ , taken together with the nitrogen atom, is N-morpholino, and Ring A is unsubstituted phenyl, then  $X^1$ ,  $X^2$ ,  $X^3$  and  $X^4$  are not, respectively:
- 1)  $CH_2$ ,  $CH(CH_2)Ph$ ,  $NR^3$ , and  $CHCH_3$ ;
  - 2)  $CH_2$ ,  $CH_2$ ,  $CH_2$ , and S;
  - 3)  $CH_2$ , S,  $CH_2$ , and S;
  - 4)  $CH_2$ ,  $CH_2$ , S, and  $CH_2$ ;
  - 5)  $CH_2$ ,  $CHMe$ , S, and  $CH_2$ ; or
  - 6)  $CHMe$ ,  $CH_2$ ,  $N(CH_2)Ph$ , and  $CH_2$ ;
- ii)  $R^1$  is not hydrogen, and  $R^2$  is not  $CH_2Ph$ ,  $(CH_2)_2O(CH_2)_2OH$ , or  $-CH_2(1,3\text{-benzodioxol-5-yl})$  when Ring A is imidazol-1-yl;
- iii) when  $R^1$  and  $R^2$ , taken together with the nitrogen atom, is N-piperidinyl then:
- 1) when  $X^1$ ,  $X^2$  and  $X^3$  are  $CH_2$ , and  $X^4$  is S, then Ring A is not unsubstituted phenyl; and
  - 2) when  $X^1$ ,  $X^2$  and  $X^4$  are  $CH_2$ ; and  $X^3$  is S, then Ring A is not unsubstituted phenyl;
- iv) when  $R^1$  and  $R^2$ , taken together with the nitrogen atom, is N-piperiziny,  $X^1$ ,  $X^2$  and  $X^3$  are  $CH_2$ ; and  $X^4$  is S, then Ring A is not 3- $NO_2Ph$ , 4-pyridinyl, or unsubstituted phenyl;
- v) when one of  $X^1$ ,  $X^2$ ,  $X^3$  or  $X^4$  is  $NR^3$  and the others of  $X^1$ ,  $X^2$ ,  $X^3$  or  $X^4$  are each  $CH_2$ , and  $R^1$  and  $R^2$  are each Me, H,  $CH_2Ph$ , or  $(CH_2)_2NMe_2$ , then Ring A is not pyrid-2-yl substituted at the 6-position;
- vi) when  $X^1$ ,  $X^2$ , and  $X^3$  are each  $CH_2$ ,  $X^4$  is S,  $R^1$  is H, and  $R^2$  is  $-CH_2-C\equiv CH$ , then Ring A is not unsubstituted phenyl;
- vii) when  $X^1$  is  $NMe$ ;  $X^2$ ,  $X^3$  and  $X^4$  are each  $CH_2$ ,  $R^1$  is H, and  $R^2$  is unsubstituted phenyl, then Ring A is not unsubstituted phenyl; and
- viii) when  $X^1$ ,  $X^2$  and  $X^4$  are each  $CH_2$ ;  $X^3$  is S,  $R^1$  and  $R^2$  are each Me, then Ring A is not unsubstituted phenyl; and
- e) when p is 0, then:
- i) when  $X^1$  is  $CH_2$ ,  $X^2$  is  $NR^3$ ,  $X^3$  is  $C=O$ ; or  $X^1$  is  $C=O$ ,  $X^2$  is  $CHR^4$ , and  $X^3$  is  $NR^3$ ; or  $X^2$  is  $NR^3$ ,  $X^2$  is  $C=O$ , and  $X^3$  is  $CHR^4$ ; or  $X^1$  is  $CH_2$ ,  $X^2$  is O, and  $X^3$  is  $C=O$ , then when  $R^1$  is hydrogen and  $R^2$  is unsubstituted phenyl or  $-CH_2CH_2Cl$ , or

when  $R^1$  and  $R^2$ , taken together form optionally substituted piperazinyl, morpholino, piperidinyl, or pyrrolidinyl, then Ring A is not optionally substituted piperidinyl, piperazinyl, morpholino, or pyrrolidinyl;

ii) when  $X^1$  is  $CHR^4$ ,  $X^2$  is  $SO_2$ , and  $X^3$  is  $CHR^4$ , and  $R^1$  and  $R^2$ , taken together are piperazinyl, then Ring A is not unsubstituted phenyl;

iii) when  $X^1$  and  $X^2$  are  $CHR^4$ ,  $X^3$  is O,  $R^1$  is hydrogen, and  $R^2$  is  $-C(=O)CH_3$ , then Ring A is not substituted furyl;

iv) when  $X^1$  is S,  $X^2$  is  $CHR^4$ ,  $X^3$  is  $CHR^4$ ; or  $X^1$  is  $CHR^4$ ,  $X^2$  is S, and  $X^3$  is  $CHR^4$ ; or  $X^1$  and  $X^2$  are  $CHR^4$  and  $X^3$  is S, then Ring A is not optionally substituted N-linked morpholino, pyrrolidinyl, piperazinyl, piperidinyl, or is not unsubstituted phenyl or cyclopropyl;

v) when  $X^1$  is  $CHR^4$ ,  $X^2$  is  $NR^3$ ,  $X^3$  is  $CHR^4$ , and  $R^1$  and  $R^2$  are both methyl, then Ring A is not 6-methyl-2-pyridyl;

vi) when  $X^1$  is  $NR^3$ ,  $X^2$  is  $C=O$ ,  $X^3$  is  $NR^3$ , and  $R^1$  and  $R^2$  are both methyl, then Ring A is not unsubstituted phenyl; and

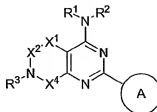
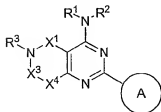
vii) when  $X^1$  and  $X^2$  are  $CHR^4$ ,  $X^3$  is  $NR^3$ ,  $R^1$  is hydrogen, and  $R^2$  is unsubstituted phenyl, then Ring A is not unsubstituted phenyl; and further provided that:

when p is 1,  $X^1$ ,  $X^2$ ,  $X^3$  and  $X^4$  are not each simultaneously  $CHR^4$ , or when p is 0,  $X^1$ ,  $X^2$ , and  $X^3$  are not each simultaneously  $CHR^4$ .

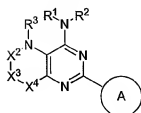
87. The compound according to claim 86, wherein p is 0 or 1.

88. The compound according to claim 86, wherein one or two of  $X^1$ ,  $X^2$ ,  $X^3$ , or  $X^4$  is  $NR^3$ , S, O, S=O, or  $SO_2$ , and the remainder each is  $CHR^4$ .

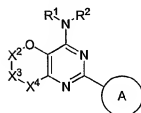
89. The compound according to claim 86, selected from:



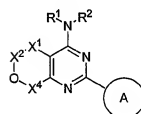
**IV-A**



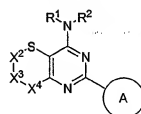
**IV-C**



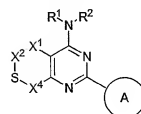
**IV-E**



**IV-G**

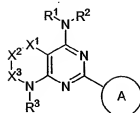


**IV-I**

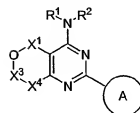


**IV-K**

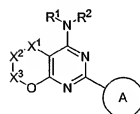
**IV-B**



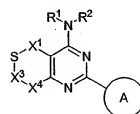
**IV-D**



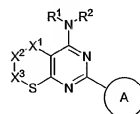
**IV-F**



**IV-H**

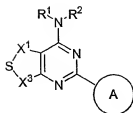


**IV-J**

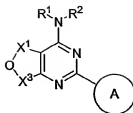


**IV-L**





IV-M



IV-N.

90. The compound according to claim 89, having formula IV-I, formula IV-J, formula IV-K, formula IV-L, or formula IV-M, wherein the sulfur ring atom is replaced with sulfoxy or sulfonyl.

91. The compound according to claim 86, wherein neither  $R^1$  nor  $R^2$  is hydrogen, and  $R^1$  and  $R^2$  are each independently selected from a 5- or 6-membered aryl ring having 0-5 heteroatoms independently selected from N, O, or S, a 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from N, O, or S, or an optionally substituted  $C_{1-4}$  aliphatic group, wherein one or more methylene units in the  $C_{1-4}$  aliphatic group are optionally and independently replaced with NR, O, (CO)O, O(CO), NR(CO), (CO)NR,  $SO_2$ (NR), or (NR) $SO_2$ .

92. The compound according to claim 86, wherein both  $R^1$  and  $R^2$  are an optionally substituted  $C_{1-4}$  aliphatic group, wherein one or more methylene units in the  $C_{1-4}$  aliphatic group are optionally and independently replaced with NR, O, (CO)O, O(CO), NR(CO), (CO)NR,  $SO_2$ (NR), or (NR) $SO_2$ .

93. The compound according to claim 92, wherein  $R^1$  and  $R^2$  are an optionally substituted  $C_{1-4}$  aliphatic group, wherein one or more methylene units in the  $C_{1-4}$  aliphatic group are optionally and independently replaced with NR, O, (CO)O, O(CO), NR(CO), (CO)NR,  $SO_2$ (NR), or (NR) $SO_2$ , preferred  $R^1$  and  $R^2$  groups are optionally substituted methyl, ethyl, cyclopropyl, n-propyl, propenyl, cyclobutyl, (CO)OCH<sub>2</sub>CH<sub>3</sub>, (CH<sub>2</sub>)<sub>2</sub>OCH<sub>3</sub>, CH<sub>2</sub>(CO)OCH<sub>2</sub>CH<sub>3</sub>, CH<sub>2</sub>(CO)OCH<sub>3</sub>, CH(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>3</sub>, or t-butyl, or n-butyl.

94. The compound according to claim 86, wherein one of  $R^1$  or  $R^2$  is hydrogen and the other of  $R^1$  or  $R^2$  is a 5-6 membered aryl ring having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

95. The compound according to claim 94, wherein one of  $R^1$  or  $R^2$  is hydrogen, and the other of  $R^1$  or  $R^2$  is an optionally substituted  $C_{1-4}$  aliphatic group, wherein one or more methylene units in the  $C_{1-4}$  aliphatic group are optionally and independently replaced with NR, O, (CO)O, O(CO), NR(CO), (CO)NR,  $SO_2$ (NR), or (NR) $SO_2$ .

96. The compound according to claim 86 or 94, wherein  $R^1$  or  $R^2$  is selected from:



a



b



c



d



e



f



g



h



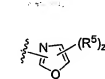
i



j



k



l



m



n



o



p



**q****r****s****t****u****v****w****x****y**

wherein each z is independently 0-4.

**z****aa****bb**

97. The compound according to claim 86, wherein  $R^1$  and  $R^2$ , taken together with the nitrogen atom to which they are bound, form an optionally substituted 3-8 membered heterocyclyl ring having 1-3 heteroatoms independently selected from nitrogen or oxygen.

98. The compound according to claim 97, wherein  $R^1$  and  $R^2$  are taken together with the nitrogen atom to which they are bound and form a 3-8 membered heterocyclyl group selected from:

**cc****dd****ee****ff****gg****hh**

wherein each z is independently 0-4.

99. The compound according to claim 98, wherein  $R^1$  and  $R^2$  taken together are optionally substituted pyrrolidin-1-yl (ff), piperidin-1-yl (dd), piperazin-1-yl (cc), or morpholin-4-yl (ee).

100. The compound according to claim 99, wherein z is 0-2.

101. The compound according to claim 100, wherein z is 0 and the ring is unsubstituted.

102. The compound according to claim 86, wherein  $R^5$  is independently halogen, CN,  $NO_2$ , or an optionally substituted group selected from  $C_{1-6}$  alkyl, aryl, aryl( $C_{1-6}$ )alkyl,  $-N(R')_2$ ,  $-CH_2N(R')_2$ ,  $OR'$ ,  $-CH_2OR'$ ,  $SR'$ ,  $-CH_2SR'$ ,  $COOR'$ ,  $-NRCOR'$ ,  $-(CH_2)_2N(R')_2$ ,  $-(CH_2)_2OR'$ ,  $-(CH_2)_2SR'$ ,  $-COR'$ ,  $-CON(R')_2$ ,  $SO_2R'$ , or  $-SO_2N(R')_2$ .

103. The compound according to claim 102, wherein  $R^5$  is independently Cl, Br, F,  $CF_3$ , Me, Et, CN,  $NO_2$ ,  $-COOH$ ,  $NH_2$ ,  $-N(CH_3)_2$ ,  $-N(Et)_2$ ,  $-N(iPr)_2$ ,  $-O(CH_2)_2OCH_3$ ,  $-CO(C_{1-4}$  alkyl),  $-CONH_2$ ,  $-COOCH_3$ ,  $-OH$ ,  $-CH_2OH$ ,  $-NHCOCH_3$ ,  $-SO_2(C_{1-4}$  alkyl),  $-SO_2NH_2$ ,  $-SO_2N(CH_3)_2$ , piperidiny, piperiziny, morpholino, or an optionally substituted group selected from  $C_{1-4}$  alkoxy, phenyl, phenyloxy, benzyl, or benzyloxy.

104. The compound according to claim 86, wherein  $R^6$  is independently hydrogen, or an optionally substituted group selected from  $C_{1-6}$  alkyl, aryl, aryl( $C_{1-6}$ )alkyl,  $-N(R')_2$ ,  $-CH_2N(R')_2$ ,  $-CH_2OR'$ ,  $-CH_2SR'$ ,  $-(CH_2)_2N(R')_2$ ,  $-(CH_2)_2OR'$ ,  $-(CH_2)_2SR'$ ,  $-COR'$ ,  $-CON(R')_2$ ,  $SO_2R'$ , or  $-S(O)_2N(R')_2$ .

105. The compound according to claim 104, wherein  $R^6$  is independently H, Me,  $CF_3$ , ethyl, propyl, butyl, pentyl,  $CO(C_{1-4}$  alkyl),  $-CONH_2$ ,  $-COO(C_{1-4}$  alkyl),  $-CH_2OH$ ,  $-SO_2(C_{1-4}$  alkyl),  $-SO_2NH_2$ ,  $SO_2N(CH_3)_2$ , or optionally substituted phenyl or benzyl.

106. The compound according to claim 86, wherein  $R^4$  is independently hydrogen, halogen, CN,  $NO_2$ , or an optionally substituted group selected from  $C_{1-6}$  alkyl, aryl, aryl( $C_{1-6}$ )alkyl, or an optionally substituted group selected from  $C_{1-6}$  alkyl, aryl, aryl( $C_{1-6}$ )alkyl,  $-N(R')_2$ ,  $-CH_2N(R')_2$ ,  $-CH_2OR'$ ,  $-CH_2SR'$ ,  $-(CH_2)_2N(R')_2$ ,  $-(CH_2)_2OR'$ ,  $-(CH_2)_2SR'$ ,  $-COR'$ ,  $-CON(R')_2$ ,  $SO_2R'$ , or  $-S(O)_2N(R')_2$ .

$\text{6)alkyl}$ ,  $-\text{N(R')}_2$ ,  $-\text{CH}_2\text{N(R')}_2$ ,  $\text{OR'}$ ,  $-\text{CH}_2\text{OR'}$ ,  $\text{SR'}$ ,  $-\text{CH}_2\text{SR'}$ ,  $\text{COOR'}$ ,  $-\text{NRCOR'}$ ,  $-(\text{CH}_2)_2\text{N(R')}_2$ ,  $-(\text{CH}_2)_2\text{OR'}$ ,  $-(\text{CH}_2)_2\text{SR'}$ ,  $-\text{COR'}$ ,  $-\text{CON(R')}_2$ ,  $\text{SO}_2\text{R'}$ , or  $-\text{SO}_2\text{N(R')}_2$ .

107. The compound according to claim 86, wherein  $\text{R}^4$  is independently H, Cl, Br, F,  $\text{CF}_3$ , Me, Et, CN,  $\text{NO}_2$ ,  $-\text{COOH}$ ,  $\text{NH}_2$ ,  $-\text{N(CH}_3)_2$ ,  $-\text{N(Et)}_2$ ,  $-\text{N(iPr)}_2$ ,  $-\text{O(CH}_2)_2\text{OCH}_3$ ,  $-\text{CO(C}_1\text{-C}_4\text{alkyl)}$ ,  $-\text{CONH}_2$ ,  $-\text{COOCH}_3$ ,  $-\text{OH}$ ,  $-\text{CH}_2\text{OH}$ ,  $-\text{NHCOCH}_3$ ,  $-\text{SO}_2(\text{C}_1\text{-C}_4\text{alkyl})$ ,  $-\text{SO}_2\text{NH}_2$ ,  $-\text{SO}_2\text{N(CH}_3)_2$ , piperidinyl, piperizinyl, morpholino, or an optionally substituted group selected from  $\text{C}_{1-4}$  alkoxy, phenyl, phenyloxy, benzyl, or benzyloxy.

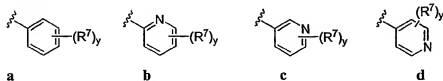
108. The compound according to claim 86, wherein  $\text{R}^3$  is independently hydrogen, or an optionally substituted group selected from  $\text{C}_{1-6}$  alkyl, aryl,  $\text{aryl(C}_{1-6}\text{)alkyl}$ ,  $-\text{N(R')}_2$ ,  $-\text{CH}_2\text{N(R')}_2$ ,  $-\text{CH}_2\text{OR'}$ ,  $-\text{CH}_2\text{SR'}$ ,  $-(\text{CH}_2)_2\text{N(R')}_2$ ,  $-(\text{CH}_2)_2\text{OR'}$ ,  $-(\text{CH}_2)_2\text{SR'}$ ,  $-\text{COR'}$ ,  $-\text{CON(R')}_2$ ,  $\text{SO}_2\text{R'}$ , or  $-\text{S(O)}_2\text{N(R')}_2$ .

109. The compound according to claim 108, wherein  $\text{R}^3$  is independently H, Me,  $\text{CF}_3$ , ethyl, propyl, butyl, pentyl,  $\text{CO(C}_1\text{-C}_4\text{alkyl)}$ ,  $-\text{CONH}_2$ ,  $-\text{COO(C}_1\text{-C}_4\text{alkyl)}$ ,  $-\text{CH}_2\text{OH}$ ,  $-\text{SO}_2(\text{C}_1\text{-C}_4\text{alkyl})$ ,  $-\text{SO}_2\text{NH}_2$ ,  $\text{SO}_2\text{N(CH}_3)_2$ , or optionally substituted phenyl or benzyl.

110. The compound according to claim 86, wherein Ring A is a 5-6 membered aryl ring having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, optionally substituted at one or more carbon atoms with 0-5 occurrences of  $-\text{R}^7$ , and at one or more substitutable nitrogen atoms with  $-\text{R}^8$ .

111. The compound according to claim 110, wherein Ring A is a phenyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, pyrrolyl, piperidinyl, indolyl, indazolyl, benzotriazolyl, pyrazolyl, benzopyrazolyl, imidazolyl, benzimidazolyl, thiazolyl, benzthiazolyl, oxazolyl, benzoxazolyl, isoxazolyl, benzisoxazolyl, isothiazolyl, benzisothiazolyl, triazolyl, benzotriazolyl, thiadiazolyl, thienyl, benzothieryl, furanoyl, benzofuranoyl, or triazinyl ring, each optionally substituted at one or more carbon atoms with 0-5 occurrences of  $-\text{R}^7$ , and at one or more substitutable nitrogen atoms with  $-\text{R}^8$ .

112. The compound according to claim 111, wherein Ring A is optionally substituted phenyl, 2-pyridyl, 3-pyridyl, or 4-pyridyl:



wherein each y is independently 0-5.

113. The compound according to claim 86, wherein  $R^7$  is independently hydrogen, halogen, CN,  $\text{NO}_2$ , or an optionally substituted group selected from  $\text{C}_{1-6}$  alkyl, aryl, aryl( $\text{C}_{1-6}$ )alkyl,  $-\text{N}(\text{R}^7)_2$ ,  $-\text{CH}_2\text{N}(\text{R}^7)_2$ ,  $\text{OR}^7$ ,  $-\text{CH}_2\text{OR}^7$ ,  $\text{SR}^7$ ,  $-\text{CH}_2\text{SR}^7$ ,  $\text{COOR}^7$ ,  $-\text{NRCOR}^7$ ,  $-(\text{CH}_2)_2\text{N}(\text{R}^7)_2$ ,  $-(\text{CH}_2)_2\text{OR}^7$ ,  $-(\text{CH}_2)_2\text{SR}^7$ ,  $-\text{COR}^7$ ,  $-\text{CON}(\text{R}^7)_2$ ,  $\text{SO}_2\text{R}^7$ , or  $-\text{SO}_2\text{N}(\text{R}^7)_2$ .

114. The compound according to claim 113, wherein  $R^7$  is independently H, Cl, Br, F,  $\text{CF}_3$ , Me, Et, CN,  $\text{NO}_2$ ,  $-\text{COOH}$ ,  $\text{NH}_2$ ,  $-\text{N}(\text{CH}_3)_2$ ,  $-\text{N}(\text{Et})_2$ ,  $-\text{N}(\text{iPr})_2$ ,  $-\text{O}(\text{CH}_2)_2\text{OCH}_3$ ,  $-\text{CO}(\text{C}_{1-4}\text{alkyl})$ ,  $-\text{CONH}_2$ ,  $-\text{COOCH}_3$ ,  $-\text{OH}$ ,  $-\text{CH}_2\text{OH}$ ,  $-\text{NHCOCH}_3$ ,  $-\text{SO}_2(\text{C}_{1-4}\text{alkyl})$ ,  $-\text{SO}_2\text{NH}_2$ ,  $-\text{SO}_2\text{N}(\text{CH}_3)_2$ , piperidinyl, piperizinyl, morpholino, or an optionally substituted group selected from  $\text{C}_{1-4}$  alkoxy, phenyl, phenyloxy, benzyl, or benzyloxy.

115. The compound according to claim 86, wherein  $R^8$  is independently hydrogen, or an optionally substituted group selected from  $\text{C}_{1-6}$  alkyl, aryl, aryl( $\text{C}_{1-6}$ )alkyl,  $-\text{N}(\text{R}^7)_2$ ,  $-\text{CH}_2\text{N}(\text{R}^7)_2$ ,  $-\text{CH}_2\text{OR}^7$ ,  $-\text{CH}_2\text{SR}^7$ ,  $-(\text{CH}_2)_2\text{N}(\text{R}^7)_2$ ,  $-(\text{CH}_2)_2\text{OR}^7$ ,  $-(\text{CH}_2)_2\text{SR}^7$ ,  $-\text{COR}^7$ ,  $-\text{CON}(\text{R}^7)_2$ ,  $\text{SO}_2\text{R}^7$ , or  $-\text{S}(\text{O})_2\text{N}(\text{R}^7)_2$ .

116. The compound according to claim 115, wherein  $R^8$  is independently H, Me,  $\text{CF}_3$ , ethyl, propyl, butyl, pentyl,  $\text{CO}(\text{C}_{1-4}\text{alkyl})$ ,  $-\text{CONH}_2$ ,  $-\text{COO}(\text{C}_{1-4}\text{alkyl})$ ,  $-\text{CH}_2\text{OH}$ ,  $-\text{SO}_2(\text{C}_{1-4}\text{alkyl})$ ,  $-\text{SO}_2\text{NH}_2$ ,  $\text{SO}_2\text{N}(\text{CH}_3)_2$ , or optionally substituted phenyl or benzyl.

117. The compound of formula IV-A according to claim 89, wherein:

$\text{R}^1$  hydrogen or methyl, and  $\text{R}^2$  is methyl, 5-methyl-pyrazol-3-yl, 5-fluoro-benzopyrazol-3-yl, or benzopyrazol-3-yl,  $\text{X}^1$ ,  $\text{X}^3$ , and  $\text{X}^4$  each is  $\text{CH}_2$ ,  $\text{R}^3$  is hydrogen, acyl, 1-oxo-2-methoxy-

ethyl, 1-oxo-propyl, methylsulfonyl, ethylsulfonyl, benzyl, and ring A is phenyl optionally substituted with halo, trifluoromethyl, hydroxy, C<sub>1-4</sub> alkyl, or C<sub>1-4</sub> alkoxy, preferably, methoxy, or ring A is 2,3-Dihydro-benzo[1,4]dioxin-3-yl.

118. The compound of formula **IV-A** according to claim 89, wherein:

R<sup>1</sup> hydrogen or methyl, and R<sup>2</sup> is methyl, 5-methyl-pyrazol-3-yl, 5-fluoro-benzopyrazol-3-yl, or benzopyrazol-3-yl, X<sup>1</sup>, X<sup>3</sup>, and X<sup>4</sup> each is CH<sub>2</sub>, R<sup>3</sup> is hydrogen or benzyl, and ring A is phenyl optionally substituted with halo, trifluoromethyl, hydroxy, C<sub>1-4</sub> alkyl, or C<sub>1-4</sub> alkoxy, preferably, methoxy, or ring A is 2,3-Dihydro-benzo[1,4]dioxin-3-yl.

119. The compound of formula **IV-A** according to claim 89, wherein:

R<sup>1</sup> hydrogen or methyl, and R<sup>2</sup> is methyl, 5-methyl-pyrazol-3-yl, 5-fluoro-benzopyrazol-3-yl, or benzopyrazol-3-yl, X<sup>1</sup>, X<sup>3</sup>, and X<sup>4</sup> each is CH<sub>2</sub>, R<sup>3</sup> is hydrogen or benzyl, and ring A is phenyl optionally substituted with halo, hydroxy or C<sub>1-4</sub> alkoxy, preferably, methoxy.

120. The compound of formula **IV-B** according to claim 89, wherein:

R<sup>1</sup> is hydrogen or methyl, R<sup>2</sup> is methyl or 5-fluorobenzimidazol-3-yl, 5-methylimidazol-3-yl, X<sup>1</sup>, X<sup>3</sup>, and X<sup>4</sup> each is CH<sub>2</sub>, R<sup>3</sup> is hydrogen, C<sub>1-4</sub> alkyl, benzyl optionally substituted with carboxy-C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkylsulfonyl, acyl, methylcarboxyethyl, C<sub>1-4</sub> alkylcarbonyl, methoxymethylcarbonyl, or benzoyl, and ring A is phenyl substituted with 2-hydroxy, 2-trifluoromethyl, 4-methyl, 4-carboxylic acid, 4-trifluoromethoxy, or 2-C<sub>1-4</sub> alkoxy, preferably, methoxy.

121. The compound of formula **IV-A** according to claim 89, wherein:

R<sup>1</sup> is hydrogen or methyl, R<sup>2</sup> is methyl or 5-fluorobenzimidazol-3-yl, X<sup>1</sup>, X<sup>3</sup>, and X<sup>4</sup> each is CH<sub>2</sub>, R<sup>3</sup> is C<sub>1-4</sub> alkyl, benzyl optionally substituted with carboxy-C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkylsulfonyl, acyl, methylcarboxyethyl, C<sub>1-4</sub> alkylcarbonyl, or benzoyl, and ring A is phenyl substituted with 2-hydroxy, 2-trifluoromethyl, or 2-C<sub>1-4</sub> alkoxy, preferably, methoxy.

122. The compound of formula **IV-B** according to claim 89, wherein:

$R^1$  and  $R^2$ , each is methyl,  $X^1$ ,  $X^3$ , and  $X^4$  each is  $CH_2$ ,  $R^3$  is  $C_{1-4}$  alkyl, benzyl optionally substituted with carboxy- $C_{1-4}$  alkyl,  $C_{1-4}$  alkylsulfonyl, or benzoyl, and ring A is phenyl substituted with 2-hydroxy or 2- $C_{1-4}$  alkoxy, preferably, methoxy.

123. The compound of formula IV-B according to claim 89, wherein:

$R^1$  and  $R^2$ , each is methyl,  $X^1$ ,  $X^3$ , and  $X^4$  each is  $CH_2$ ,  $R^3$  is  $C_{1-4}$  alkyl, or benzyl optionally substituted with carboxy- $C_{1-4}$  alkyl, and ring A is phenyl substituted with 2-hydroxy or 2- $C_{1-4}$  alkoxy, preferably, methoxy.

124. The compound of formula IV-B according to claim 89, wherein:

$R^1$  and  $R^2$ , each is methyl,  $X^1$ ,  $X^3$ , and  $X^4$  each is  $CH_2$ ,  $R^3$  is  $C_{1-4}$  alkyl, benzyl optionally substituted with carboxy- $C_{1-4}$  alkyl,  $C_{1-4}$  alkoxy, and ring A is 2-hydroxy phenyl or 2- $C_{1-4}$  alkoxyphenyl.

125. The compound of formula IV-B according to claim 89, wherein:

$R^1$  and  $R^2$ , each is methyl,  $X^1$ ,  $X^3$ , and  $X^4$  each is  $CH_2$ ,  $R^3$  is benzyl optionally substituted with carboxy- $C_{1-4}$  alkyl,  $C_{1-4}$  alkoxy, and ring A is 2-hydroxy phenyl.

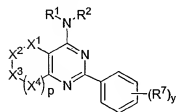
126. The compound of formula IV-M according to claim 89, wherein:

$R^1$  is hydrogen or methyl, and  $R^2$  is methyl, benzimidazol-3-yl, 5-methyl-imidazol-3-yl, ring A is 2-hydroxyphenyl, 2-fluorophenyl, 2-trifluoromethylphenyl or phenyl.

127. The compound of formula IV-M according to claim 89, wherein:

$R^1$  is hydrogen or methyl, and  $R^2$  is methyl, benzimidazol-3-yl, 5-methyl-imidazol-3-yl, ring A is 2-trifluoromethylphenyl or phenyl.

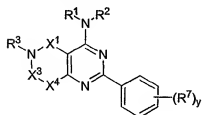
128. The compound according to claim 87, wherein said compound has formula V:



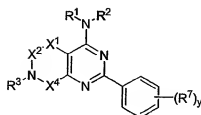
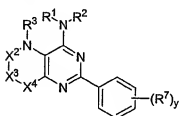


V.

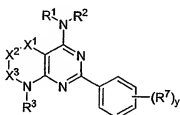
129. The compound according to claim 128, wherein said compound has one of the following structures:



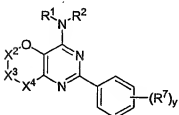
V-A



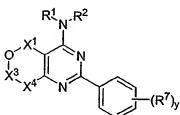
V-B



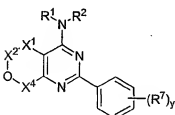
V-C



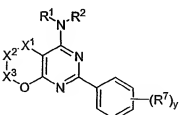
V-D



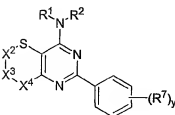
V-E



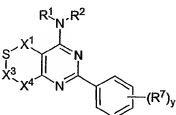
V-F



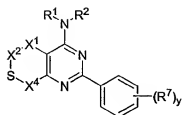
V-G



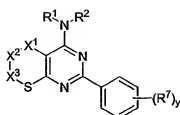
V-H



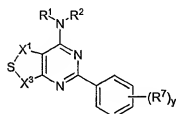
V-I



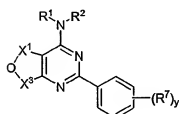
V-J



V-K



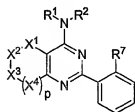
V-L



V-M

V-N

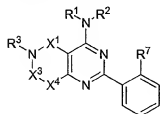
130. The compound according to claim 128, wherein said compound has formula VI:



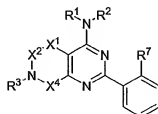
VI

wherein  $R^7$  is halogen,  $CN$ ,  $NO_2$ , or an optionally substituted group selected from  $C_{1-4}$  alkyl, aryl, aralkyl,  $-N(R')$ ,  $-CH_2N(R')$ ,  $-OR'$ ,  $-CH_2OR'$ ,  $-SR'$ ,  $-CH_2SR'$ ,  $-COOR'$ ,  $-NRCOR'$ ,  $-CON(R')$ , or  $-S(O)_2N(R')$ .

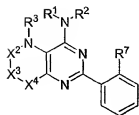
131. The compound according to claim 130, wherein said compound has a structure selected from formulae VI-A through VI-N:



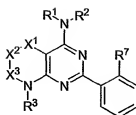
VI-A



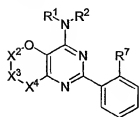
VI-B



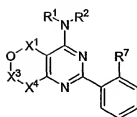
VI-C



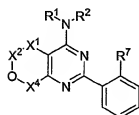
VI-D



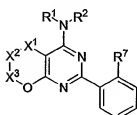
VI-E



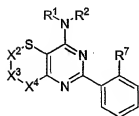
VI-F



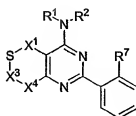
VI-G



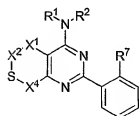
VI-H



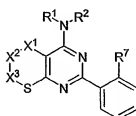
VI-I



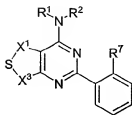
VI-J



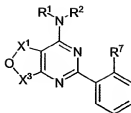
VI-K



VI-L



VI-M



VI-N.

132. The compound to claim 131, wherein:

- a.  $R^1$  and  $R^2$  are each independently selected from a 5- or 6-membered aryl ring having 0-5 heteroatoms independently selected from N, O, or S; a 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from N, O, or S; or an optionally substituted  $C_{1-4}$  aliphatic group, wherein one or more methylene units in the  $C_{1-4}$  aliphatic group are optionally and independently replaced with NR, O, (CO)O, O(CO), NR(CO), (CO)NR,  $SO_2$ (NR), or (NR) $SO_2$ ;
- b. each occurrence of  $R^3$  is independently hydrogen, or an optionally substituted group selected from  $C_{1-6}$  alkyl, aryl, aryl( $C_{1-6}$ )alkyl,  $-N(R')_2$ ,  $-CH_2N(R')_2$ ,  $-CH_2OR'$ ,  $-CH_2SR'$ ,  $-(CH_2)_2N(R')_2$ ,  $-(CH_2)_2OR'$ ,  $-(CH_2)_2SR'$ ,  $-COR'$ ,  $-CON(R')_2$ ,  $SO_2R'$ , or  $-S(O)_2N(R')_2$ ; and
- c. each occurrence of  $R^4$  is independently hydrogen, halogen, CN,  $NO_2$ , or an optionally substituted group selected from  $C_{1-6}$  alkyl, aryl, aryl( $C_{1-6}$ )alkyl,  $-N(R')_2$ ,  $-CH_2N(R')_2$ ,  $OR'$ ,  $-CH_2OR'$ ,  $SR'$ ,  $-CH_2SR'$ ,  $COOR'$ ,  $-NRCOR'$ ,  $-(CH_2)_2N(R')_2$ ,  $-(CH_2)_2OR'$ ,  $-(CH_2)_2SR'$ ,  $-COR'$ ,  $-CON(R')_2$ ,  $SO_2R'$ , or  $-SO_2N(R')_2$ .

133. The compound according to claim 131, wherein:

- a.  $R^1$  and  $R^2$  are each independently optionally substituted methyl, ethyl, cyclopropyl, n-propyl, propenyl, cyclobutyl, (CO)OCH<sub>2</sub>CH<sub>3</sub>, (CH<sub>2</sub>)<sub>2</sub>OCH<sub>3</sub>, CH<sub>2</sub>(CO)OCH<sub>2</sub>CH<sub>3</sub>, CH<sub>2</sub>(CO)OCH<sub>3</sub>, CH(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>3</sub>, or t-butyl, or n-butyl;
- b. each occurrence of  $R^3$  is independently H, Me, CF<sub>3</sub>, ethyl, propyl, butyl, pentyl, CO( $C_{1-4}$ alkyl),  $-CONH_2$ ,  $-COO(C_{1-4}$ alkyl),  $-CH_2OH$ ,  $-SO_2(C_{1-4}$ alkyl),  $-SO_2NH_2$ ,  $SO_2N(CH_3)_2$ , or optionally substituted phenyl or benzyl; and

e. each occurrence of  $R^4$  is independently H, Cl, Br, F,  $CF_3$ , Me, Et, CN,  $NO_2$ ,  $-COOH$ ,  $NH_2$ ,  $-N(CH_3)_2$ ,  $-N(Et)_2$ ,  $-N(iPr)_2$ ,  $-O(CH_2)_2OCH_3$ ,  $-CO(C_1-C_4alkyl)$ ,  $-CONH_2$ ,  $-COOCH_3$ ,  $-OH$ ,  $-CH_2OH$ ,  $-NHCOCH_3$ ,  $-SO_2(C_1-C_4alkyl)$ ,  $-SO_2NH_2$ ,  $-SO_2N(CH_3)_2$ , piperidinyl, piperizinyl, morpholino, or an optionally substituted group selected from  $C_{1-4}$  alkoxy, phenyl, phenyloxy, benzyl, or benzyloxy.

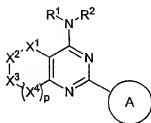
134. The compound according to claim 131, wherein:

- a.  $R^1$  and  $R^2$  are each independently optionally substituted methyl, ethyl, cyclopropyl, n-propyl, propenyl, cyclobutyl,  $(CO)OCH_2CH_3$ ,  $(CH_2)_2OCH_3$ ,  $CH_2(CO)OCH_2CH_3$ ,  $CH_2(CO)OCH_3$ ,  $CH(CH_3)CH_2CH_3$ , or t-butyl, or n-butyl;
- b. each occurrence of  $R^3$  is independently H, Me,  $CF_3$ , ethyl, propyl, butyl, pentyl,  $CO(C_1-C_4alkyl)$ ,  $-CONH_2$ ,  $-COO(C_1-C_4alkyl)$ ,  $-CH_2OH$ ,  $-SO_2(C_1-C_4alkyl)$ ,  $-SO_2NH_2$ ,  $SO_2N(CH_3)_2$ , or optionally substituted phenyl or benzyl;
- c. each occurrence of  $R^4$  is independently H, Cl, Br, F,  $CF_3$ , Me, Et, CN,  $NO_2$ ,  $-COOH$ ,  $NH_2$ ,  $-N(CH_3)_2$ ,  $-N(Et)_2$ ,  $-N(iPr)_2$ ,  $-O(CH_2)_2OCH_3$ ,  $-CO(C_1-C_4alkyl)$ ,  $-CONH_2$ ,  $-COOCH_3$ ,  $-OH$ ,  $-CH_2OH$ ,  $-NHCOCH_3$ ,  $-SO_2(C_1-C_4alkyl)$ ,  $-SO_2NH_2$ ,  $-SO_2N(CH_3)_2$ , piperidinyl, piperizinyl, morpholino, or an optionally substituted group selected from  $C_{1-4}$  alkoxy, phenyl, phenyloxy, benzyl, or benzyloxy; and
- d.  $R^7$  is Cl, Br, F,  $CF_3$ , Me, Et, CN,  $NO_2$ ,  $-COOH$ ,  $NH_2$ ,  $-N(CH_3)_2$ ,  $-N(Et)_2$ ,  $-N(iPr)_2$ ,  $-O(CH_2)_2OCH_3$ ,  $-CO(C_1-C_4alkyl)$ ,  $-CONH_2$ ,  $-COOCH_3$ ,  $-OH$ ,  $-CH_2OH$ ,  $-NHCOCH_3$ ,  $-SO_2(C_1-C_4alkyl)$ ,  $-SO_2NH_2$ ,  $-SO_2N(CH_3)_2$ , piperidinyl, piperizinyl, morpholino, or an optionally substituted group selected from  $C_{1-4}$  alkoxy, phenyl, phenyloxy, benzyl, or benzyloxy.

135. A pharmaceutical composition comprising a compound according to claim 1 or 15, and a pharmaceutically acceptable carrier or adjuvant.

136. A method of treating or lessening the severity of a disease, disorder, or condition selected from acute, chronic, neuropathic, or inflammatory pain, arthritis, migraine, cluster headaches, trigeminal neuralgia, herpetic neuralgia, general neuralgias, epilepsy or epileptic conditions, neurodegenerative disorders, psychiatric disorders such

as anxiety and depression, myotonia, arrhythmia, movement disorders, neuroendocrine disorders, ataxia, multiple sclerosis, irritable bowel syndrome, incontinence, visceral pain, osteoarthritis pain, postherpetic neuralgia, diabetic neuropathy, radicular pain, sciatica, back pain, head or neck pain, severe or intractable pain, nociceptive pain, breakthrough pain, postsurgical pain, or cancer pain, comprising the step of administering to said patient an effective amount of a compound according of formula I:



I

or a pharmaceutically acceptable salt thereof, wherein:

p is 0, 1 or 2;

X<sup>1</sup>, X<sup>2</sup>, X<sup>3</sup> and X<sup>4</sup> are each independently selected from NR<sup>3</sup>, C=O, CHR<sup>4</sup>, S, O, S=O, or SO<sub>2</sub>;

R<sup>1</sup> and R<sup>2</sup> are each independently hydrogen, or an optionally substituted group selected from C<sub>1-6</sub> aliphatic, a 5-6 membered aryl ring having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or R<sup>1</sup> and R<sup>2</sup>, taken together with the nitrogen atom to which they are bound, form an optionally substituted 3-8 membered heterocyclyl or heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein R<sup>1</sup>, R<sup>2</sup>, or any ring formed by R<sup>1</sup> and R<sup>2</sup> taken together, are each independently optionally substituted at one or more carbon atoms with 0-4 occurrences of -R<sup>5</sup>, and at one or more substitutable nitrogen atoms with -R<sup>6</sup>;

Ring A is a 5-6 membered monocyclic or 8-10 membered bicyclic aryl ring having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, optionally substituted at one or more carbon atoms with 0-5 occurrences of -R<sup>7</sup>, and at one or more substitutable nitrogen atoms with -R<sup>8</sup>;

each occurrence of  $R^4$ ,  $R^5$ , and  $R^7$  is independently  $Q-R^X$ ; wherein Q is a bond or is a  $C_1$ - $C_6$  alkylidene chain wherein up to two non-adjacent methylene units of Q are optionally and independently replaced by CO,  $CO_2$ , COCO, CONR, OCONR, NRNR, NRNRCO, NRCO,  $NRCO_2$ , NRCONR, SO,  $SO_2$ ,  $NRSO_2$ ,  $SO_2NR$ ,  $NRSO_2NR$ , O, S, or NR;

each occurrence of  $R^X$  is independently selected from  $R'$ , halogen,  $NO_2$ , or CN;

each occurrence of R is independently selected from hydrogen or an optionally substituted  $C_{1-6}$  aliphatic group;

each occurrence of  $R'$  is independently selected from hydrogen or an optionally substituted group selected from  $C_{1-8}$  aliphatic,  $C_{6-10}$  aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclyl ring having 3-10 ring atoms, or wherein R and  $R'$  taken together with the atom(s) to which they are bound, or two occurrences of  $R'$  taken together with the atom(s) to which they are bound, form a 5-8 membered cycloalkyl, heterocyclyl, aryl, or heteroaryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and

each occurrence of  $R^3$ ,  $R^6$  or  $R^8$  is independently  $R'$ ,  $-COR'$ ,  $-CO_2(C_{1-6} \text{ aliphatic})$ ,  $-CON(R')_2$ , or  $-SO_2R'$ .

137. The method according to claim 136, wherein said compound is according to claim 1 or 15.

138. The method according to claim 136, wherein the disease, condition, or disorder is implicated in the activation or hyperactivity of voltage-gated sodium channels.

139. The method according to claim 136, wherein the disease, condition, or disorder is implicated in the activation or hyperactivity of voltage-gated calcium channels.

140. The method according to claim 139, wherein the disease, condition, or disorder is acute, chronic, neuropathic, or inflammatory pain.

141. The method according to claim 136, wherein the disease, condition, or disorder is radicular pain, sciatica, back pain, head pain, or neck pain.

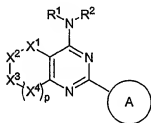
142. The method according to claim 136, wherein the disease, condition, or disorder is severe or intractable pain, acute pain, post-surgical pain, back pain, or cancer pain.

143. A method of inhibiting one or more of NaV1.1, NaV1.2, NaV1.3, NaV1.4, NaV1.5, NaV1.6, NaV1.7, NaV1.8, NaV1.9, or CaV2.2 activity in:

(a) a patient; or

(b) a biological sample;

which method comprising administering to said patient, or contacting said biological sample with a compound of formula I:



I

or a pharmaceutically acceptable salt thereof, wherein:

p is 0, 1 or 2;

X<sup>1</sup>, X<sup>2</sup>, X<sup>3</sup> and X<sup>4</sup> are each independently selected from NR<sup>3</sup>, C=O, CHR<sup>4</sup>, S, O, S=O, or SO<sub>2</sub>;

R<sup>1</sup> and R<sup>2</sup> are each independently hydrogen, or an optionally substituted group selected from C<sub>1-6</sub> aliphatic, a 5-6 membered aryl ring having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or R<sup>1</sup> and R<sup>2</sup>, taken together with the nitrogen atom to which they are bound, form an optionally substituted 3-8 membered heterocyclyl or heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein R<sup>1</sup>, R<sup>2</sup>, or any ring formed by R<sup>1</sup> and R<sup>2</sup> taken together, are each independently optionally substituted at one or more carbon atoms with 0-4 occurrences of -R<sup>5</sup>, and at one or more substitutable nitrogen atoms with -R<sup>6</sup>;



Ring A is a 5-6 membered monocyclic or 8-10 membered bicyclic aryl ring having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, optionally substituted at one or more carbon atoms with 0-5 occurrences of  $-R^7$ , and at one or more substitutable nitrogen atoms with  $-R^8$ ;

each occurrence of  $R^4$ ,  $R^5$ , and  $R^7$  is independently  $Q-R^X$ ; wherein Q is a bond or is a  $C_1-C_6$  alkylidene chain wherein up to two non-adjacent methylene units of Q are optionally and independently replaced by CO,  $CO_2$ , COCO, CONR, OCONR, NRNR, NRNRCO, NRCO, NR $CO_2$ , NRCONR, SO,  $SO_2$ , NRSO $_2$ ,  $SO_2NR$ , NRSO $_2NR$ , O, S, or NR;

each occurrence of  $R^X$  is independently selected from  $R'$ , halogen,  $NO_2$ , or CN;

each occurrence of R is independently selected from hydrogen or an optionally substituted  $C_{1-6}$  aliphatic group;

each occurrence of  $R'$  is independently selected from hydrogen or an optionally substituted group selected from  $C_{1-8}$  aliphatic,  $C_{6-10}$  aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclyl ring having 3-10 ring atoms, or wherein R and  $R'$  taken together with the atom(s) to which they are bound, or two occurrences of  $R'$  taken together with the atom(s) to which they are bound, form a 5-8 membered cycloalkyl, heterocyclyl, aryl, or heteroaryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and each occurrence of  $R^3$ ,  $R^6$  or  $R^8$  is independently  $R'$ ,  $-COR'$ ,  $-CO_2(C_{1-6} \text{ aliphatic})$ ,  $-CON(R')_2$ , or  $-SO_2R'$ .

144. The method according to claim 143, wherein said compound is according to claim 1 or 15.

145. The method according to claim 136 or 143, wherein said compound is selected from Table 1.

146. A compound selected from Table 1.

# INTERNATIONAL SEARCH REPORT

ational Application No.  
.../US2004/025559

**A. CLASSIFICATION OF SUBJECT MATTER**  
 IPC 7 C07D239/94 C07D403/04 A61K31/517 C07D401/04 C07D403/12  
 C07D401/14 C07D405/12 C07D471/04 A61P29/00 A61P25/00  
 C07D495/04

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
 IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data, BEILSTEIN Data, PAJ

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03/049739 A1 (VERTEX PHARMACEUTICALS, INC., USA) 19 June 2003 (2003-06-19) claim 23; examples 108-113	1-135
X	US 5 972 946 A (MURATA, TERUYA ET AL) 26 October 1999 (1999-10-26) 2nd and 6th compounds of Table 3, col.11	1-135
X	JP 07 228573 A (DAINIPPON PHARMACEUTICAL CO, JAPAN) 29 August 1995 (1995-08-29) col.15-16, page 9, compound 6 in Table	1-135
X	JP 04 224580 A (NIPPON SODA CO., LTD., JAPAN) 13 August 1992 (1992-08-13) compound n°25, col.25-26, p.14	1-135
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*Z\* document member of the same patent family

Date of the actual completion of the international search

30 November 2004

Date of mailing of the international search report

09/12/2004

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 Fax: (+31-70) 340-3016

Authorized officer

Schuemacher, A

## INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US2004/025559

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 276 057 A (MERCK AND CO., INC., USA) 27 July 1988 (1988-07-27) 4th compound in Table p. 4	1-135
X	US 4 886 807 A (KITAMURA, NORIHIKO ET AL) 12 December 1989 (1989-12-12) compound 13, col. 12, 1.44-45	1-135
X	US 3 346 452 A (DE STEVENS GEORGE ET AL) 10 October 1967 (1967-10-10) 5,6-(1,5-pentylene)-2-phenyl-4N-(2-(4-thia morpholino)-pyrimidine, col. 14, 1.63-64	1-135
X	FR 1 455 810 A (THOMAE GMBH DR K) 20 May 1966 (1966-05-20) examples 57-88, 94, 98-100, 125-131	1-135
X	US 3 316 257 A (GERHARD OHNACKER) 25 April 1967 (1967-04-25) col. 7-8, ex. (ee), (ff), (hh), (ii), (jj)	1-135
X	GB 1 048 986 A (THOMAE GMBH DR K) 23 November 1966 (1966-11-23) examples p.13-26	1-135
X	US 3 248 395 A (GERHARD OHNACKER) 26 April 1966 (1966-04-26) examples; claims 2,5	1-135
X	FR 2 450 M (DR. K. THOMAE) 6 April 1964 (1964-04-06) the whole document	1-135
X	OHNO S ET AL: "SYNTHESIS AND HYPOGLYCEMIC ACTIVITY OF 7,8-DIHYDRO-6H-THIOPYRANOU3,2- DPYRIMIDINE DERIVATIVES AND RELATED COMPOUNDS" CHEMICAL AND PHARMACEUTICAL BULLETIN, PHARMACEUTICAL SOCIETY OF JAPAN, vol. 34, no. 10, 1 October 1986 (1986-10-01), pages 4150-4165, XP000196068 ISSN: 0009-2363 compounds 131 and 130 in Table II	1-135
X	DATABASE BEILSTEIN 'Online! BEILSTEIN INSTITUTE FOR ORGANIC CHEMISTRY, FRANKFURT-MAIN, DE; XP002305900 Database accession no. 6927325 (BRN) 4-amino-2-phenyl-5,6,7,8-tetrahydroquinazo line-5-one & IZV. AKAD. NAUK. SSSR SER. KHIM., vol. 8, 1993, pages 1504-1505,	1-135

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## INTERNATIONAL SEARCH REPORT

ational Application No

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE BEILSTEIN 'Online!  BEILSTEIN INSTITUTE FOR ORGANIC CHEMISTRY,  FRANKFURT-MAIN, DE;  XP002305901  Database accession no. 76781-45-8 (CAS-RN)  2-piperazinyl-yl-6,7,8,9-tetrahydro-5H-cycl  oheptapyrimidin-4-ylamine  &amp; EUR.J.MED.CHEM.CHIM.THER.,  vol. 15, no. 4, 1980, pages 317-322,</p>	1-135
Y	<p>PASTOR: "Synthesis and Structure of New  Pyrido(2,3-d)pyrimidine Derivatives with  Calcium Channel Antagonist Activity"  TETRAHEDRON, ELSEVIER SCIENCE PUBLISHERS,  vol. 50, no. 27, 1994, pages 8085-8098,  XP002092648  ISSN: 0040-4020  the whole document</p>	1-146
Y	<p>ARRANZ E ET AL: "Synthesis and  pharmacological evaluation of  2,3-dihydro-3-oxo-4H-thien  o'3,4-e'1,2,4-thiadiazine 1,1-dioxides as  voltage-dependent calcium channel  blockers"  EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY,  EDITIONS SCIENTIFIQUE ELSEVIER,  vol. 35, no. 7-8, August 2000 (2000-08),  pages 751-759, XP004372929  ISSN: 0223-5234  the whole document</p>	1-146
Y	<p>WO 03/037900 A (GROSS MICHAEL FRANCIS ;  VAN RHEE MICHEL ALBERT (US); ICAGEN INC  (US);) 8 May 2003 (2003-05-08)  claims 1-4</p>	1-146
A	<p>US 6 372 740 B1 (MURATA, TERUYA ET AL)  16 April 2002 (2002-04-16)  claims 1,15,18</p>	1-146

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US2004/025559

## Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Although claims 136-145 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

RU1/US2004/025559

Patent document cited in search report		Publication date		Patent family member(s)	Publication date
WO 03049739	A1	19-06-2003	CA EP US	2469316 A1 1474147 A1 2003199526 A1	19-06-2003 10-11-2004 23-10-2003
US 5972946	A	26-10-1999	AT AU AU BR CA CN CZ DE DE DK EP ES HU IL WO NO NZ PL PT RO RU SK TW ZA	228113 T 694647 B2 5287496 A 9604894 A 2218033 A1 1186487 A , B 9703223 A3 69624916 D1 69624916 T2 826673 T3 0826673 A1 2187644 T3 9801688 A2 117659 A 9632383 A1 974685 A 304982 A 322819 A1 826673 T 117532 B1 2160256 C2 137497 A3 450963 B 9602438 A	15-12-2002 23-07-1998 30-10-1996 14-07-1998 17-10-1996 01-07-1998 18-02-1998 02-01-2003 24-04-2003 24-03-2003 04-03-1998 16-06-2003 29-03-1999 06-12-2000 17-10-1996 12-12-1997 29-03-1999 16-02-1998 28-02-2003 30-04-2002 10-12-2000 06-05-1998 21-08-2001 01-10-1996
JP 7228573	A	29-08-1995	NONE		
JP 4224580	A	13-08-1992	NONE		
EP 0276057	A	27-07-1988	US US AT CA DE DE DK EP IE JP US	4871739 A 4889856 A 102625 T 1308410 C 3888215 D1 3888215 T2 23088 A 0276057 A2 880139 L 63192778 A 4994464 A	03-10-1989 26-12-1989 15-03-1994 06-10-1992 14-04-1994 08-09-1994 22-07-1988 27-07-1988 21-07-1988 10-08-1988 19-02-1991
US 4886807	A	12-12-1989	JP JP JP AT DE EP	1855719 C 5059118 B 60226882 A 51231 T 3576690 D1 0163599 A2	07-07-1994 30-08-1993 12-11-1985 15-04-1990 26-04-1990 04-12-1985
US 3346452	A	10-10-1967	US	3322759 A	30-05-1967
FR 1455810	A	20-05-1966	CH CH DE FR	510048 A 469737 A 1470354 A1 4320 M	15-07-1971 15-03-1969 09-10-1969

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
FR 1455810	A	GB 1075188 A US 3311623 A	12-07-1967 28-03-1967
US 3316257	A 25-04-1967	CH 441344 A CH 441346 A DE 1251765 B FR 3773 M FR 1555461 A GB 1065317 A	15-08-1967 15-08-1967  31-01-1969 12-04-1967
GB 1048986	A 23-11-1966	NL 6504085 A DE 1470336 A1 US 3272811 A US 3318881 A US 3318883 A BE 663693 A FR 3761 M NL 123139 C	03-10-1966 20-03-1969 13-09-1966 09-05-1967 09-05-1967
US 3248395	A 26-04-1966	DE 1197466 B CH 437327 A CH 462186 A GB 1033384 A	29-07-1965 15-06-1967 15-09-1968 22-06-1966
FR 2450	M	NONE	
WO 03037900	A 08-05-2003	CA 2465326 A1 WO 03037900 A2 US 2003176450 A1	08-05-2003 08-05-2003 18-09-2003
US 6372740	B1 16-04-2002	AT 248169 T AU 744014 B2 AU 1260499 A BR 9815140 A CA 2312885 A1 CN 1284076 T DE 69817611 D1 DE 69817611 T2 DK 1036794 T3 EP 1036794 A1 ES 2205574 T3 HK 1028769 A1 HU 0004422 A2 ID 24929 A WO 9928320 A1 NO 20002835 A NZ 504457 A PL 340925 A1 PT 1036794 T RU 2223272 C2 SI 1036794 T1 SK 7972000 A3 TR 200001600 T2 TW 502034 B ZA 9810490 A	15-09-2003 14-02-2002 16-06-1999 10-10-2000 10-06-1999 14-02-2001 02-10-2003 26-02-2004 22-12-2003 20-09-2000 01-05-2004 24-12-2003 28-04-2001 31-08-2000 10-06-1999 24-07-2000 21-12-2001 12-03-2001 28-11-2003 10-02-2004 31-12-2003 12-03-2001 21-11-2000 11-09-2002 20-05-1999